**Department of Medicinal Chemistry**
**Faculty of Pharmacy**
**Mansoura University**

# Anticancer Drugs

**Hussein I. El-Subbagh, Ph.D.**
subbagh@yahoo.com
http://hussein-i-el-subbagh-phd.webs.com/
http://www.scopus.com/authid/detail.url?authorId=7004304572

# Introduction

- **The diversity of tumors and the similarity to normal cells are the main obstacle preventing the reach of an ultimate remedy.**
- **The main task of anticancer drug is to destruct malignant cells, while sparing normal cells.**
- **Cancers could be classified according to their nature and location throughout the human body into two main categories: Solid tumors such as glandular tissue cancers, connective tissue cancers. Malignant hematologic diseases such as lymphatic ganglia and blood cancers.**
- **Tumors can be classified according to their locations into:**
  - **Carcinoma → Glandular tissue cancers.**
  - **Sarcoma → Connective tissue cancers.**
  - **Lymphoma → Lymphatic ganglia cancers.**
  - **Leukemia → Blood cancers.**

- **Solid tumors are difficult to treat due to the lack of vascularity and blood supply inside the tumor, which prevents any drug from reaching the core of the tumor mass.**
- **The rate of cell division is the only sensible difference (found so far) which distinct cancer cell from normal cell, tumor cell is rapidly proliferating.**
- **The lack of obvious difference makes it difficult for any chemotherapeutic agent to distinguish between cancer cell and any healthy cell, especially those which are naturally of rapid cell division, as for example hair, bone marrow cells and the mucosa linening the walls of the gastrointestinal tract.**

***How could the anticancer agents be selectively toxic to cancer cell?***

- **Tumor cell is more rapidly proliferating than normal cell so it will consume more of the drug. But the drug is highly toxic to the organs which is normally rapidly proliferating such as bone marrow, hair, GIT.**

- **Anticancer agents could be classified based on type of activity into three main groups:**

1) **Growth inhibitors: Drugs which inhibit the growth of cancer cells into 50%.**

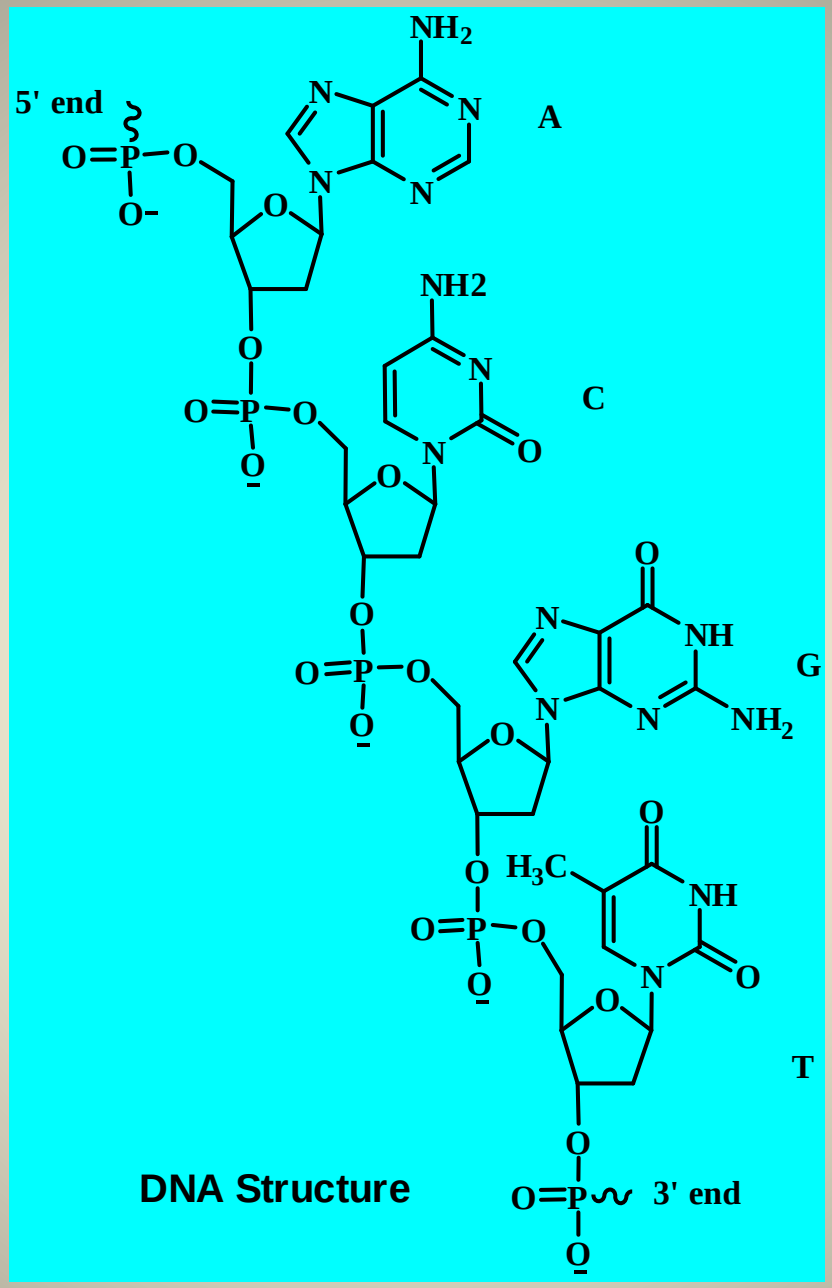
   **Median growth inhibitory concentration ($GI_{50}$): Molar concentration which inhibit net cell growth to 50%.**

2) **Cytostatic agents: Drugs which totally inhibit the growth of cancer cells.**

   **Total growth inhibitory concentration (TGI): Molar concentration which cause total inhibition of cell growth.**

3) **Cytotoxic agents: Drugs which cause 50% killing of the original no. of cancer cells.**

   **Median lethal concentration ($LC_{50}$): Molar concentration which cause 50% killing of the initial cell level**


5' end
A
C
G
T
DNA Structure
3' end

# Cancer Chemotherapy

- **The difference between normal and cancerous cell lies in the cell nucleus which controls cell division and rather more, it might reach the gene level.**
- **Most of the antineoplastic agents are designed to interfere with the protein synthesis followed by the inhibition of cell vital processes leading to cell death.**
- **Anticancer agents could be classified based on their mode of action into:**
    1. **DNA Interactive Drugs (DID)**
    2. **Antimetabolites**
    3. **Hormones**

# I. DNA Interactive Drugs (DID)

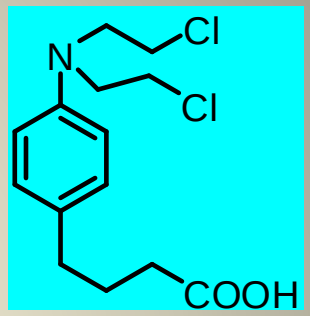
## A. DNA Alkylators

- **DNA alkylators are those class of compounds which proved to alkylate the nucleophilic centers at the nucleic acid bases (guanine, thymine … etc.) leading to the formation of deformed DNA which will affect protein synthesis causing cell death.**
- **DNA alkylators could be classified into:**

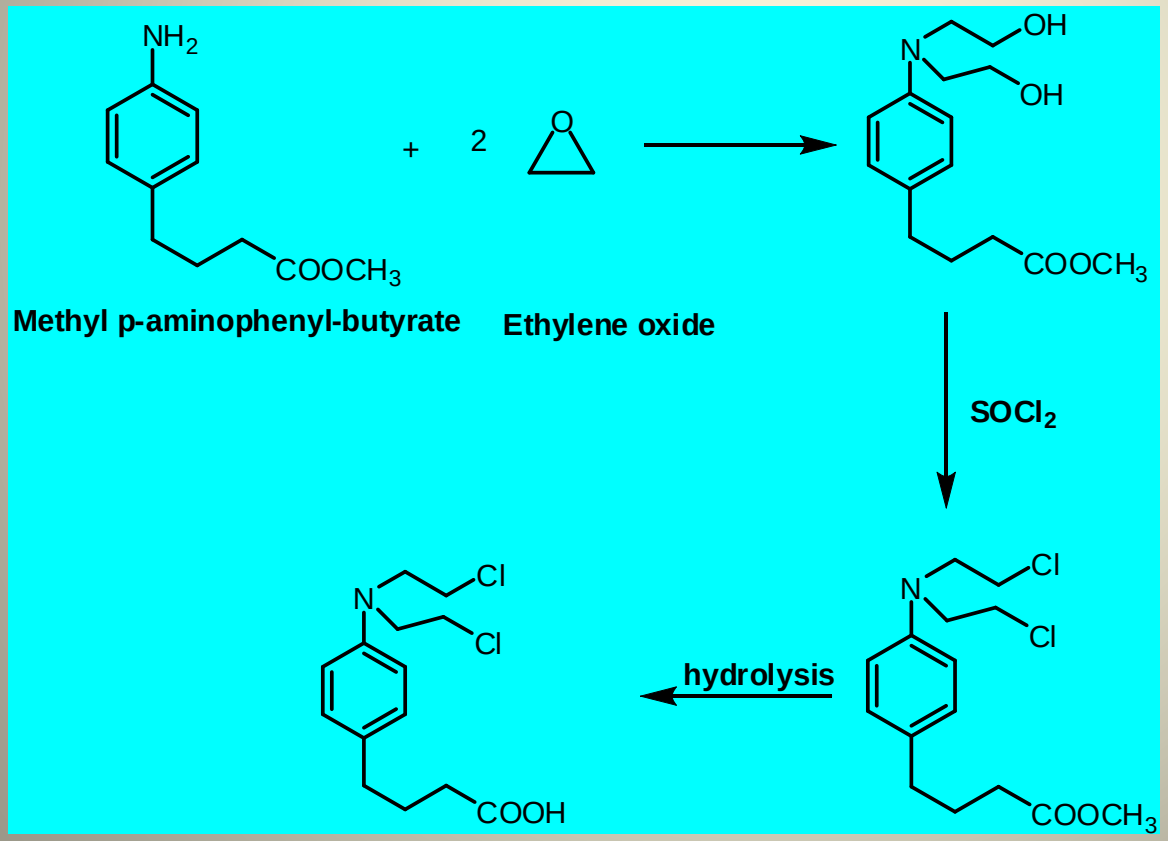
a. **Nitrogen mustard and its analogues.**
b. **Ethylenimines.**
c. **Epoxides.**
d. **Sulphonic acid esters.**
e. **Miscellaneous.**

# Nitrogen Mustards

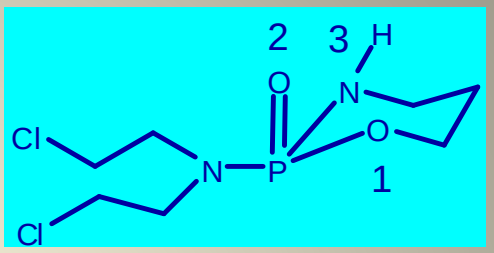
## 1. Chlorambucil, Leukeran




**4-[Bis-(2-chloroethyl)amine]phenylbutyric acid.**

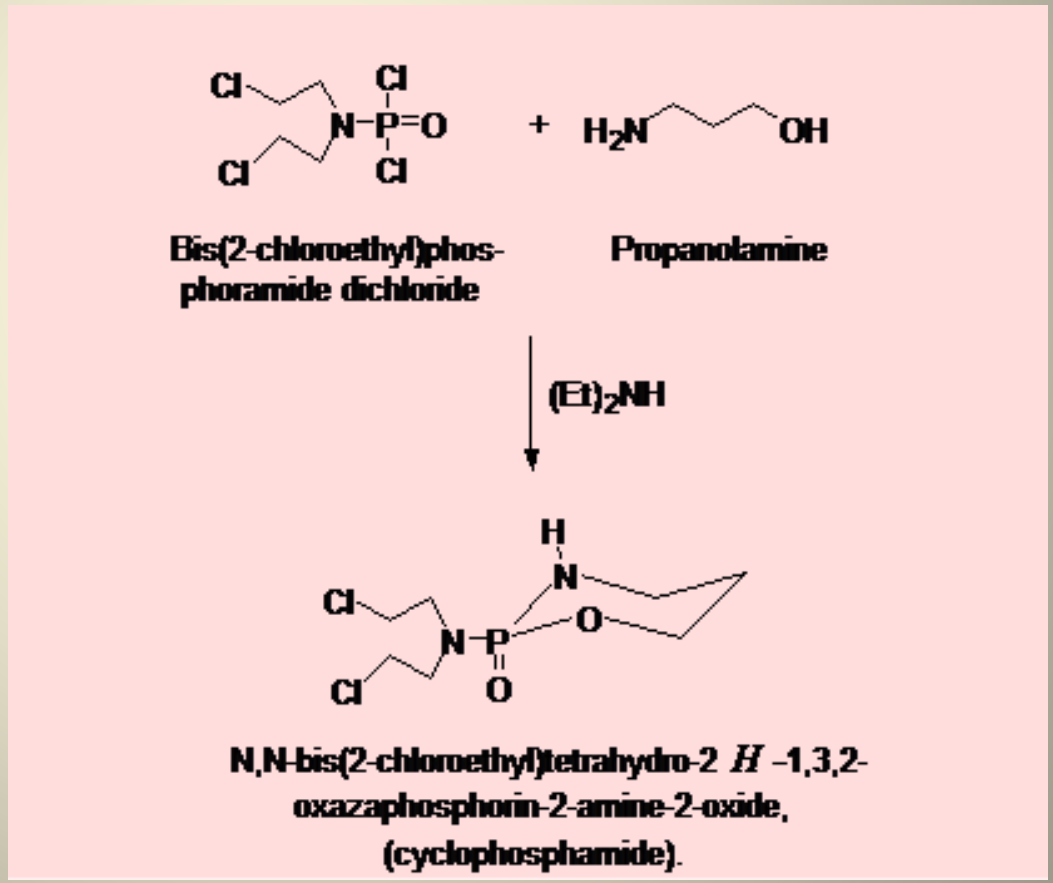


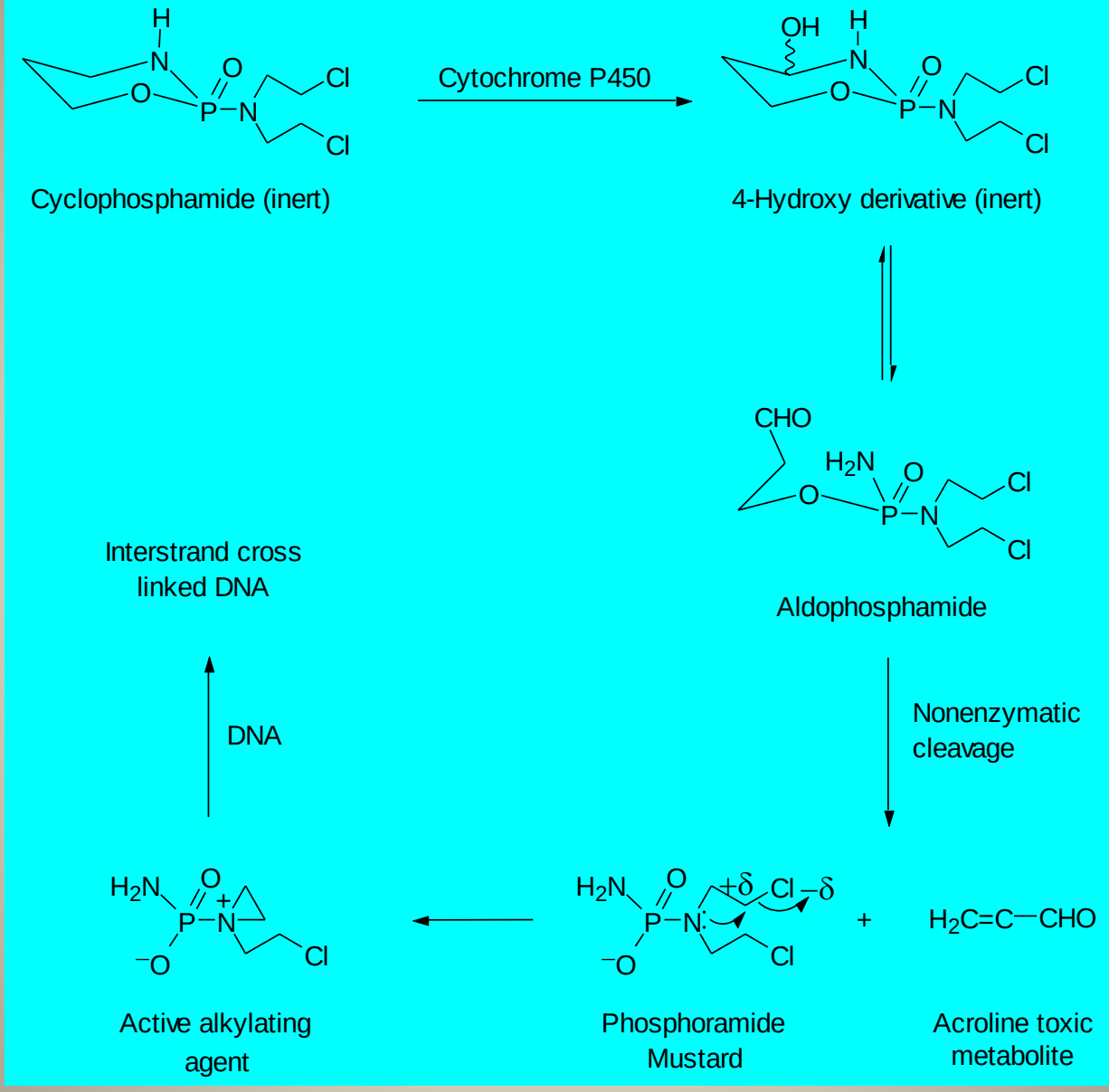
## 2. Cyclophosphamide, Cytoxan, Endoxan



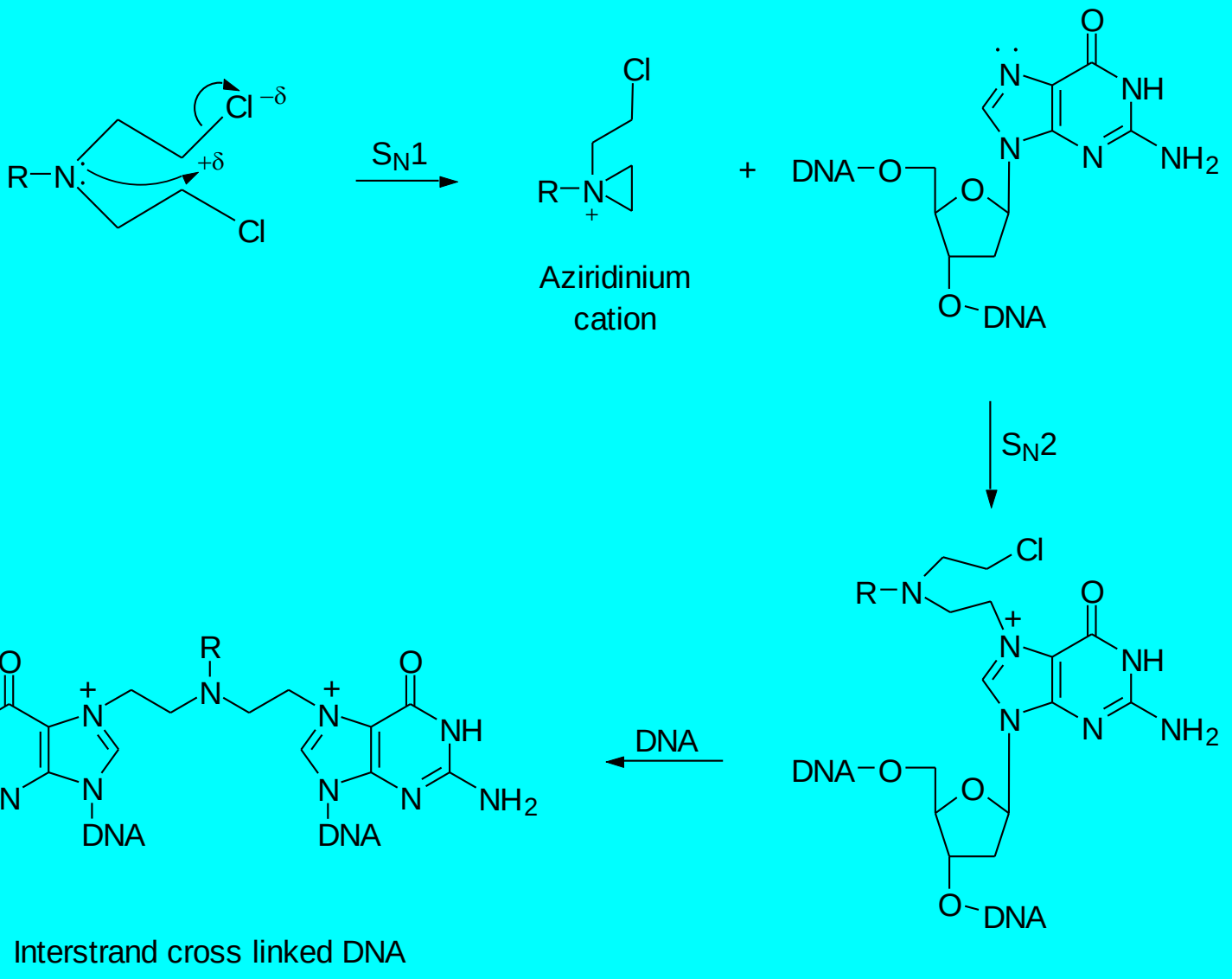

**N,N-*Bis*(2-chloroethyl)tetrahydro-2*H*-1,3,2-oxazaphosphorin-2-amine-2-oxide.**

**Synthesis**




Cyclophosphamide (inert)
Cytochrome P450
4-Hydroxy derivative (inert)
Aldophosphamide
Nonenzymatic cleavage
Phosphoramide Mustard
Acroline toxic metabolite
Active alkylating agent
DNA
Interstrand cross linked DNA

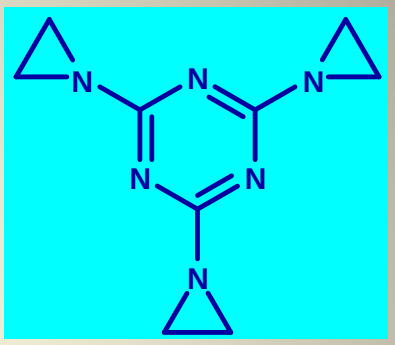
# Mode of Action of Nitrogen Mustards




Interstrand cross linked DNA

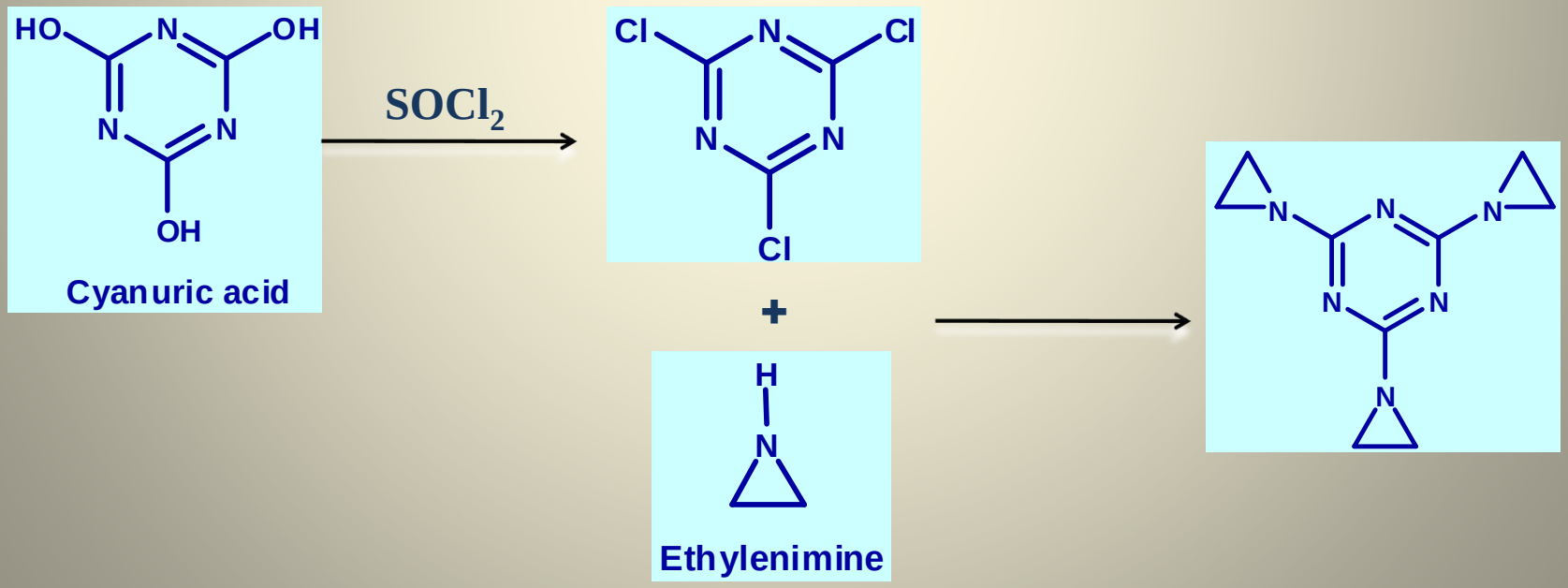
# Ethylenimine Derivatives

## 1. Triethylene melamine (TEM)



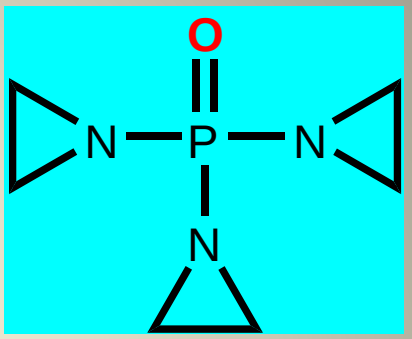
**2,4,6-Tris (1-aziridinyl)-s-triazine.**

**Synthesis**

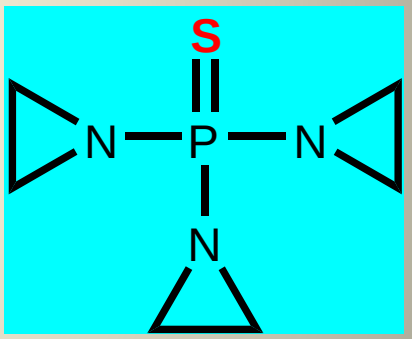


## 2. Phosphoramide Derivatives

**Triethylene phosphoramide (TEPA)**

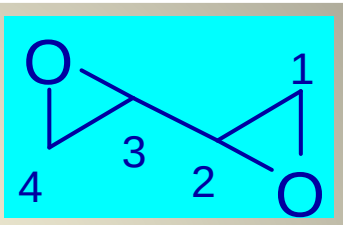



**Triethylene thiophosphoramide (thio-TEPA)**

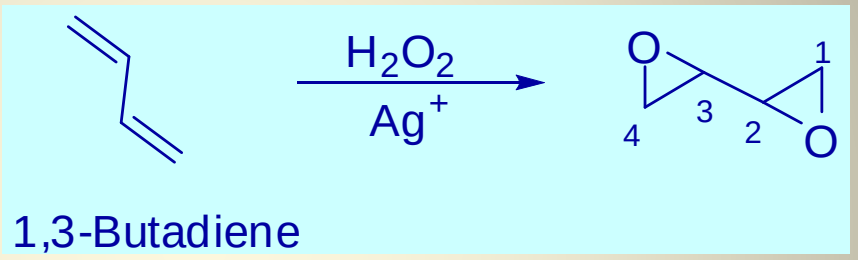


# Epoxides

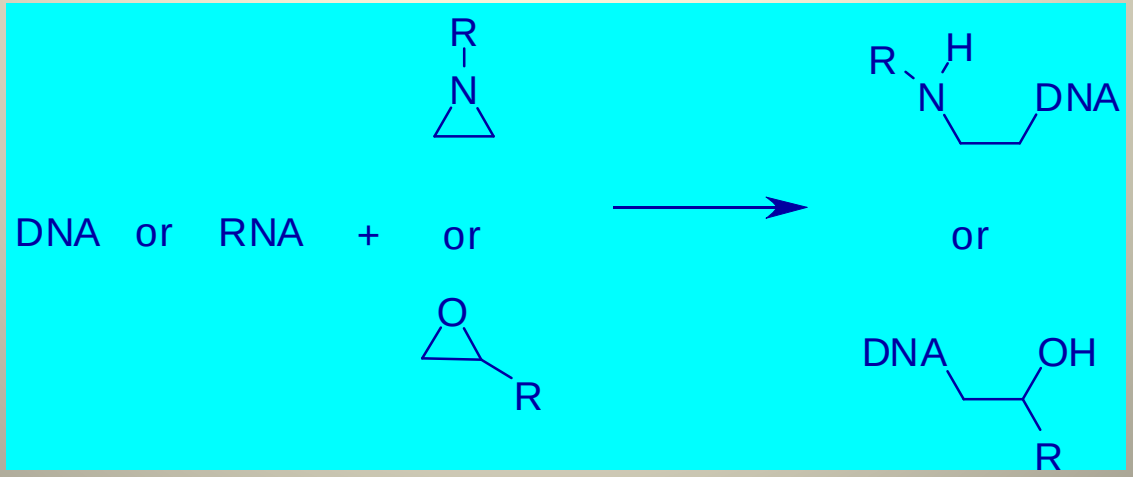
## 1,2,3,4-Diepoxybutane




**Synthesis**

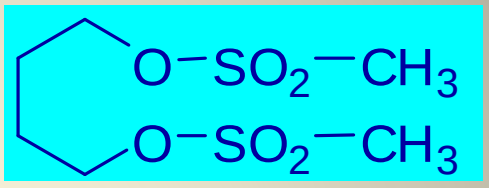



## Mode of Action of Ethylenimines and Epoxides



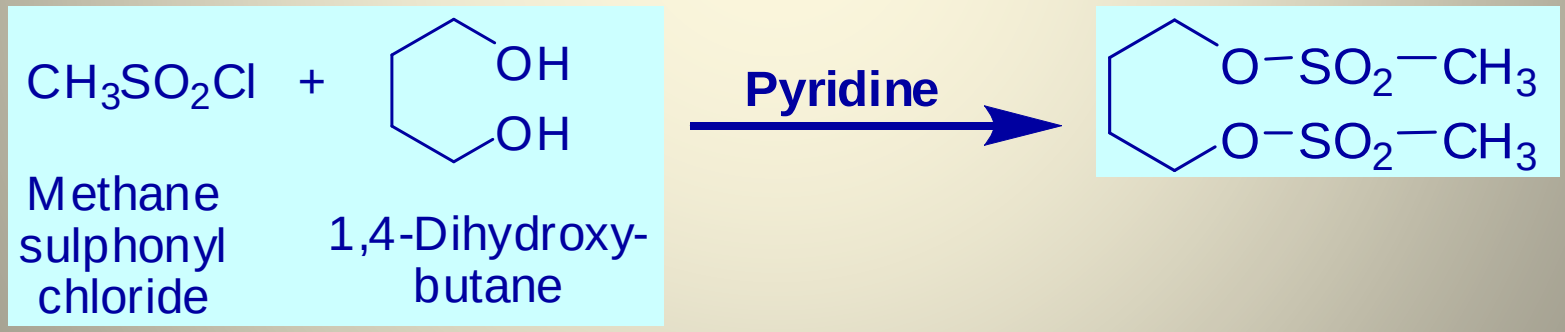
# Sulphonic Acid Esters

**Busulfan, Myleran**

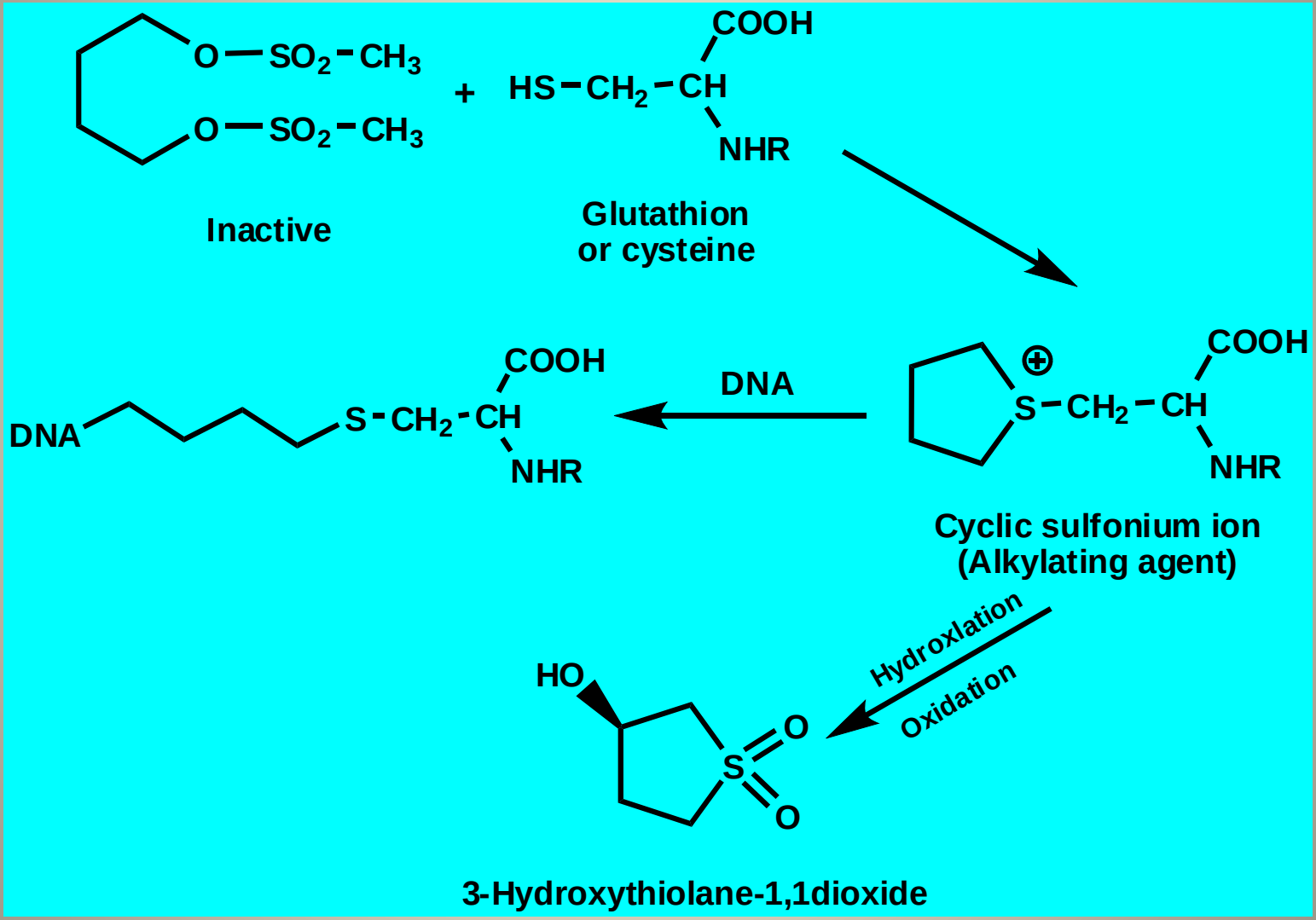



**1,4-Di(Methan-sulphonyl-oxy)butane**

**Synthesis**

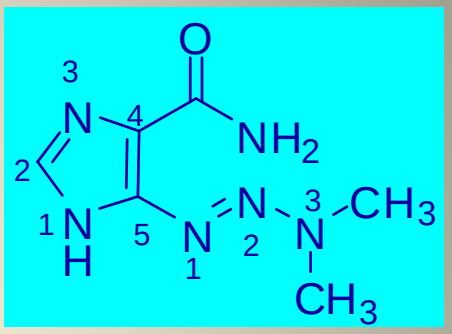


# Metabolism and Mode of Action



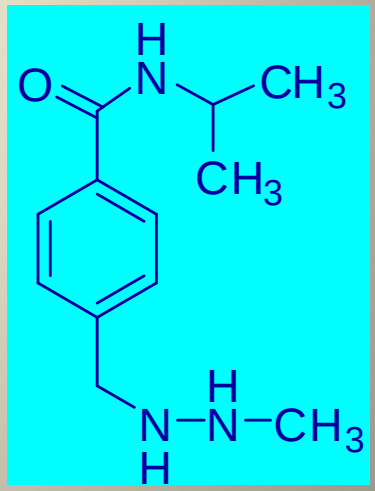
# Miscellaneous

## 1. Dacarbazine, DTIC



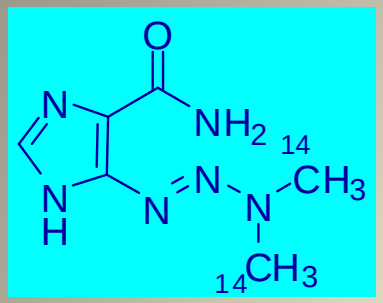

**5-(3,3-Dimethyl-1-triazino)-imidazole-4-carboxamide**

## 2. Procarbazine HCl, Matulane



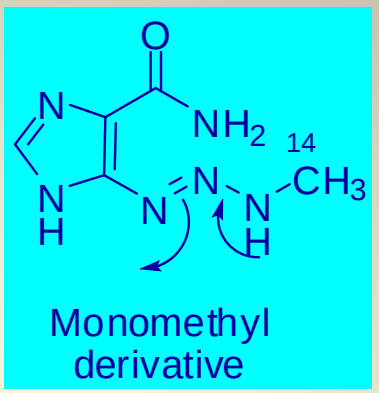

**N-(Isopropyl)-4-(2-methyl-hydrazino-methyl)benzamide**

# Metabolism and Mode of Action



Oxidative dealkylation

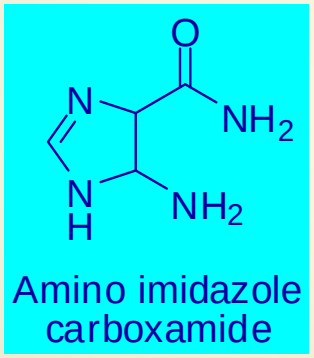
Cytochrome P-450



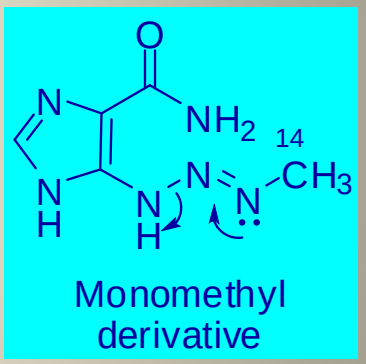
Monomethyl derivative

Diazomethane cytotoxic (moiety)

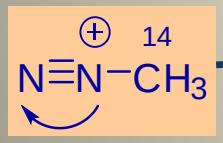
+

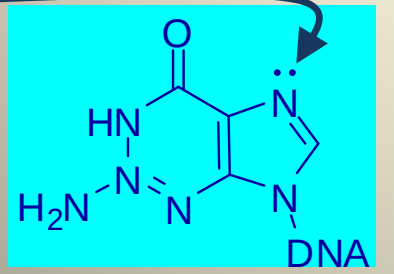


Amino imidazole carboxamide



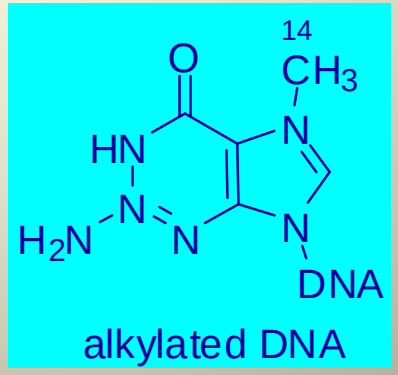
Monomethyl derivative





DNA

$-N_2$



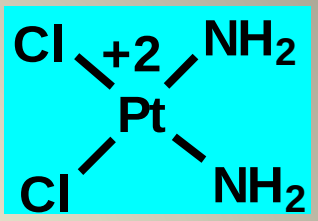
alkylated DNA

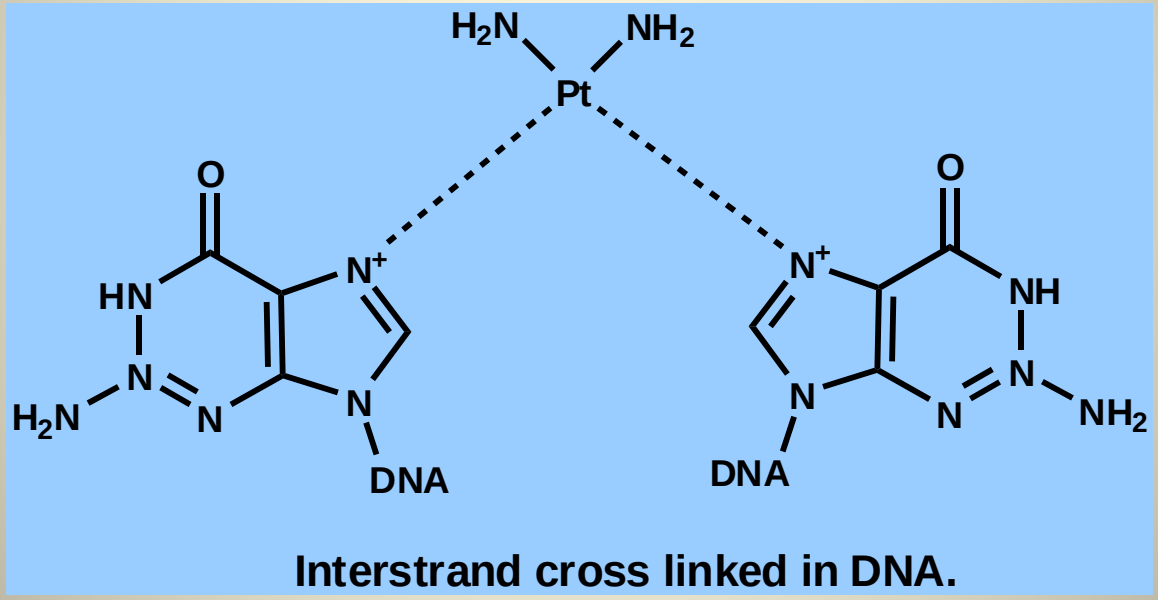
**Cell Death**

# 3. Platinum Compounds

**Cisplatin, Platinol,**

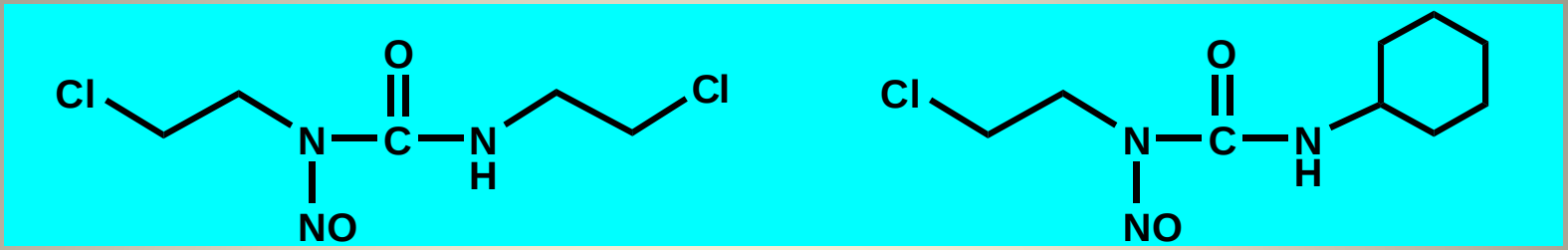
**Diaminedichloroplatinum**




Interstrand cross linked in DNA.

## 4. Nitrosoureas




**Carmustine (BCNU)**
**1,3-Bis(2-chloroethyl)-1-nitrosourea**

**Lumustine (CCNU)**
**1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea**

- **Duration of Action:**

**BCNU: t ½ = 90 min.** **CCNU: t ½ = 16 hr.**

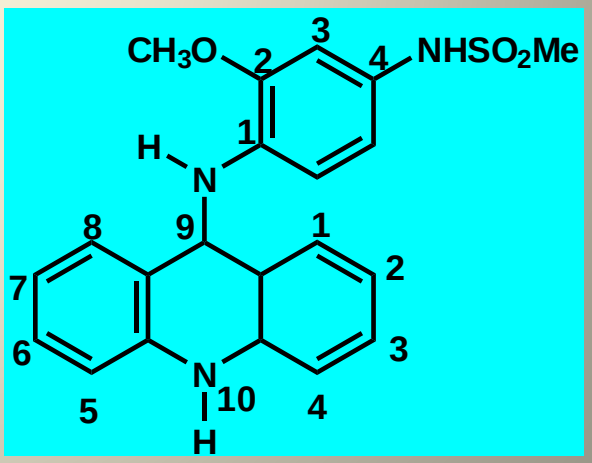
- **Nitrosoureas possess high lipid solubility which allows BBB crossing, so they used mainly to treat Brain tumors**

# B. Groove Binding Agents (DNA Intercalators)

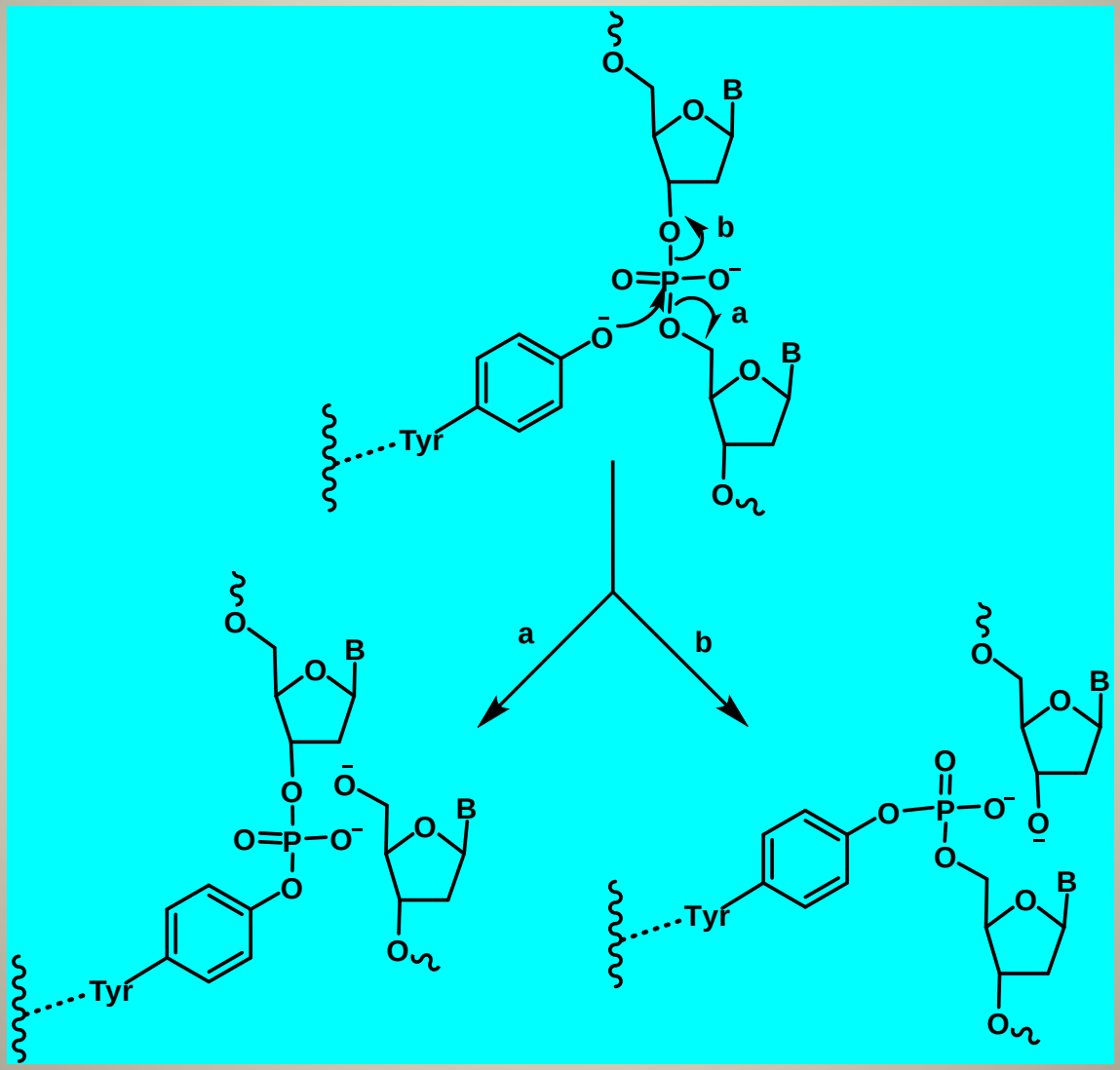
- **Polycyclic plannar compounds have the ability to insert or intercalate through the grooves of the base pairs of the DNA double helix.**
- **This insertion process will activate Topoisomerase I & II enzymatic system which catalyzes DNA strand cleavage.**
- **Acridines such as Amsacrine proved to possess this DNA intercalation activity.**

## Amsacrine

**9-[(2-Methoxy-4-methylsulphonylamino) aniline]acridine.**



- **The tyrosinyl moiety carried by Topoisomerases could catalyze such DNA cleavage.**



# C. DNA Strand Breakers

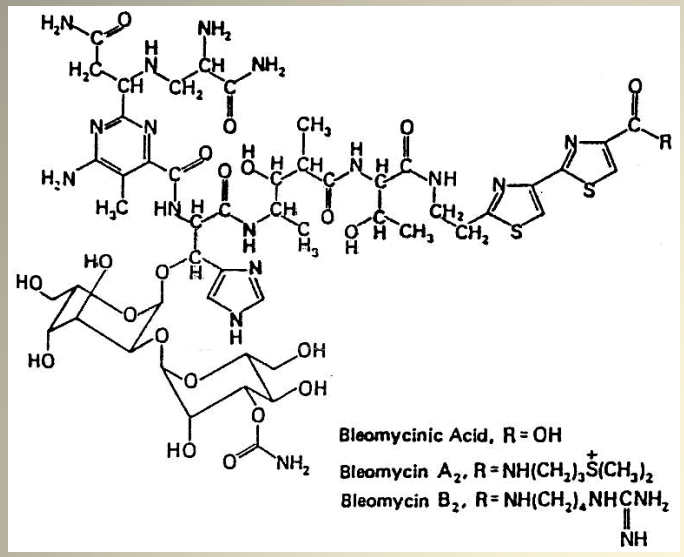
- **A group of natural products are characterized by their ability to intercalate into the DNA and initiate a series of free radical destruction of the DNA strand preventing the process of mitosis and consequently preventing cell division.**

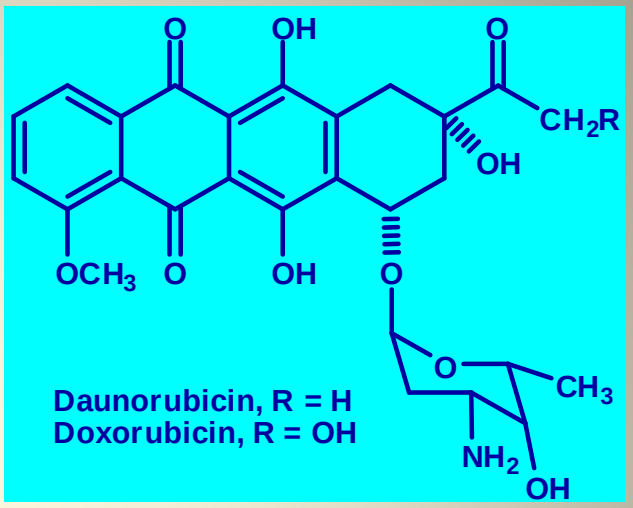
- **Those Natural products are:**
  - **Antibiotics**

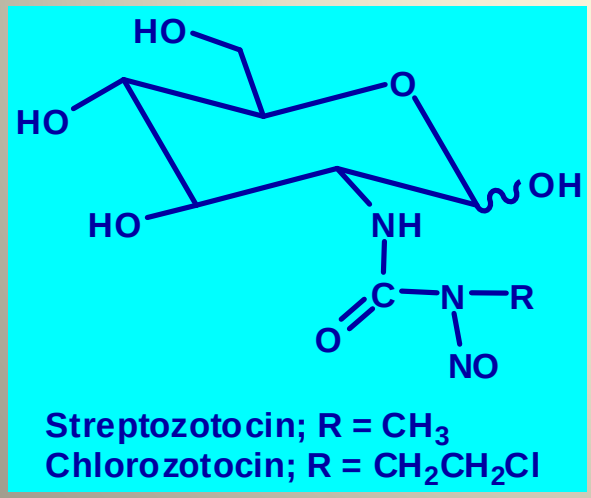
    **Bleomycins, Daunorubicins, Mitomycins, Streptozotocin**
  - **Vinca Alkaloids**

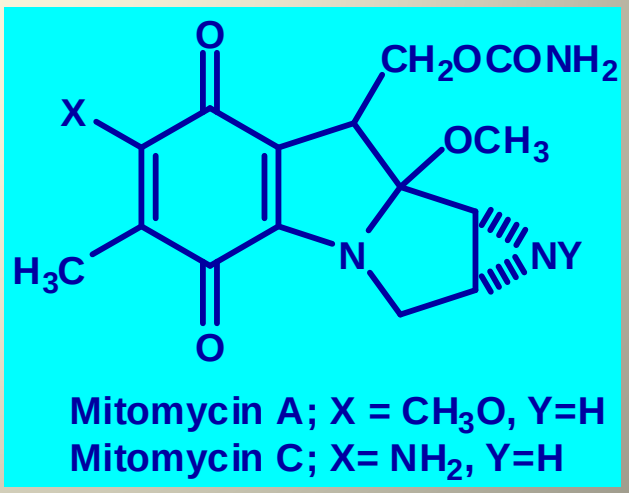
    **Vinblastine, Vincristine**

# ❖ Antibiotics



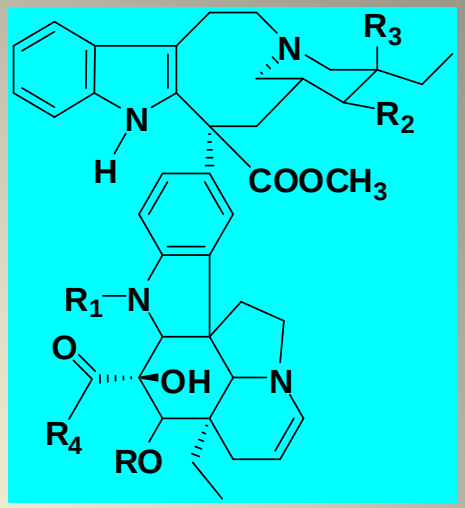



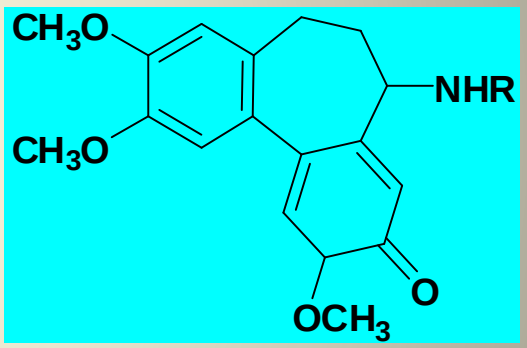
❖ **Vinca Alkaloids and their Analogs**

**Vincrestin**

**Vinblastin**



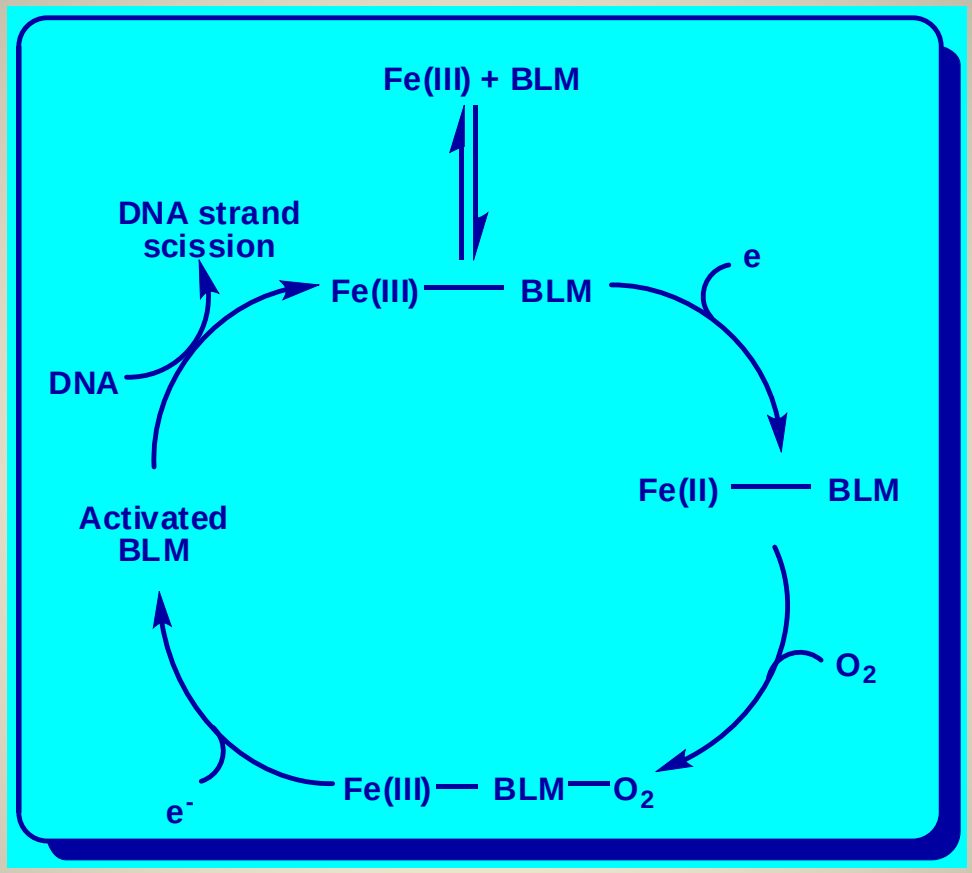

- **Colchicine, obtained from Colchicum autumnale, Its main use is in terminating acute attacks of gout.**
- **Colchicines have an unusual tricyclic structure containing a tropolone ring.**
- **Colchicines and it derivative demecolcine (colcemid) is active against myelocytic leukemia.**
- **They inhibit mitosis at metaphase by disorienting the organization of the mytotic spindle.**




**Colchicine, R = $COCH_3$**

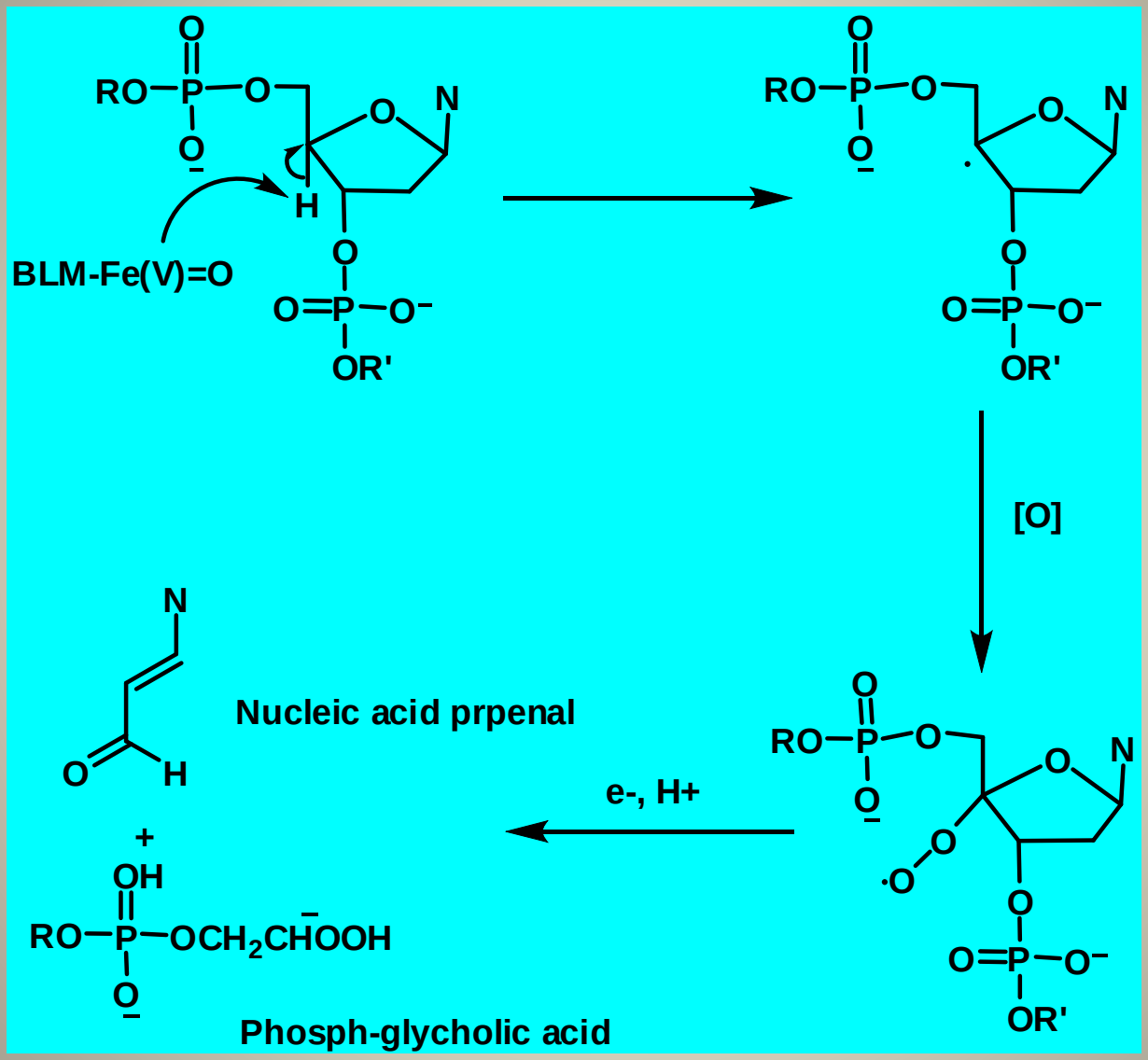
**Colcemid, R = $CH_3$**

# Mode of Action of Strand Breakers




**Cycle of events involved in DNA cleavage by bleomycin (BLM)**

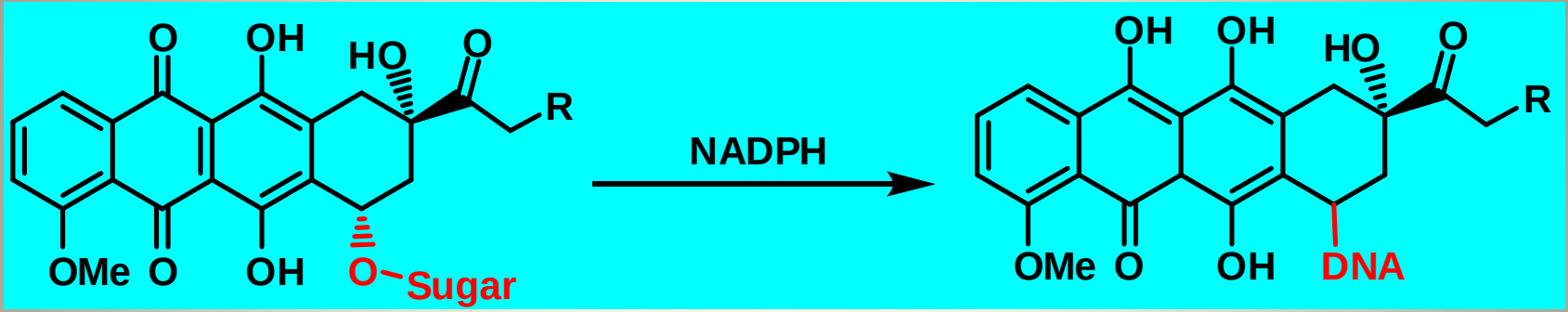
# DNA strand Scission by Activated Bleomycin



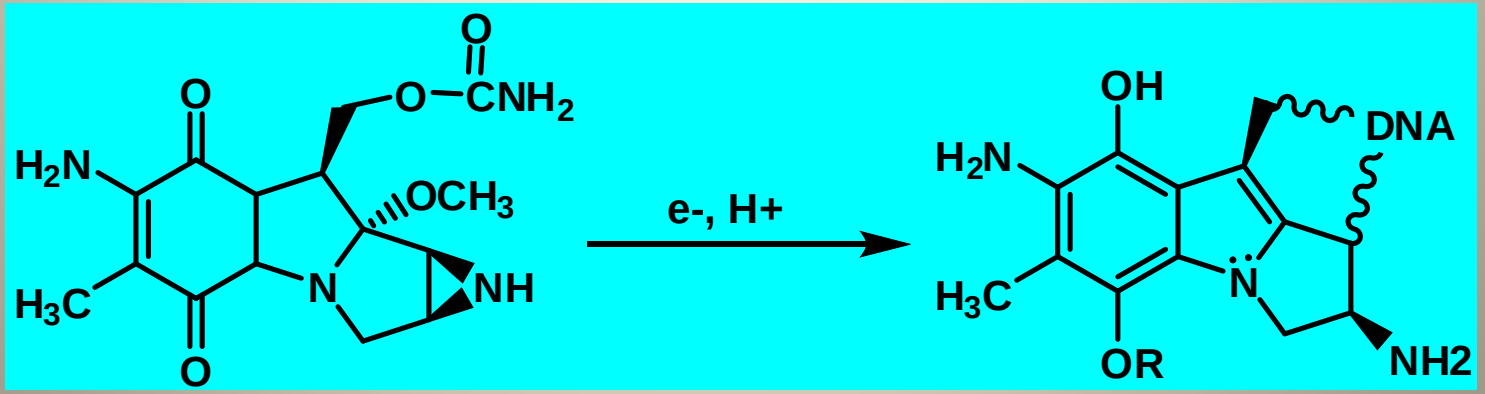
# Mode of Action of Antimitotic Agents

## i. Daunorubicin Analogs

**Anthracycline antitumor agents as bioreductive alkylators**




## ii. Mitomycin analogs



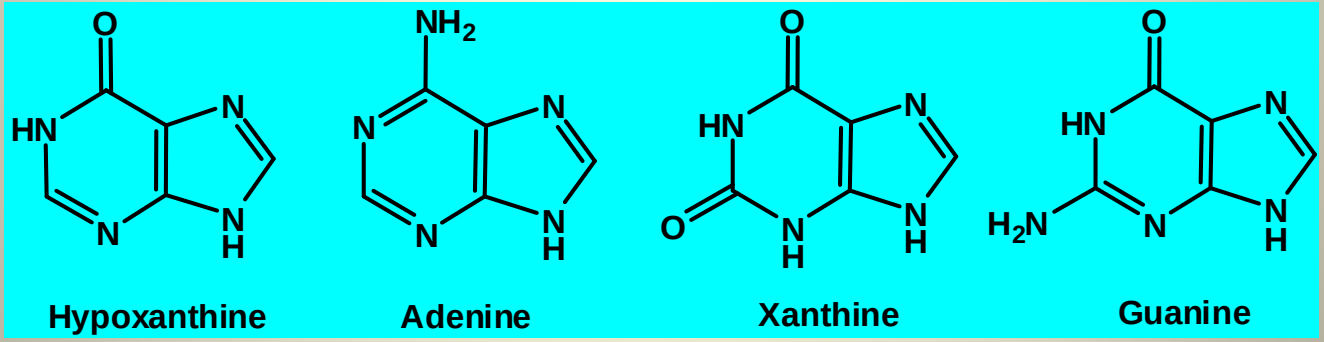
# II. Antimetabolites

- **Those are class of compounds which are structurally related to natural occurring substances found in normal cells.**
- **Antimetabolites compete with those natural cell components for the active sites on enzyme(s) or receptor(s), and they might incorporate into the nucleic acids to disrupt their cellular functions.**
- **Antimetabolites could be classified into:**

  **A. Purine Antagonists**
  **B. Pyrimidine Antagonists**
  **C. Folic acid Antagonists**

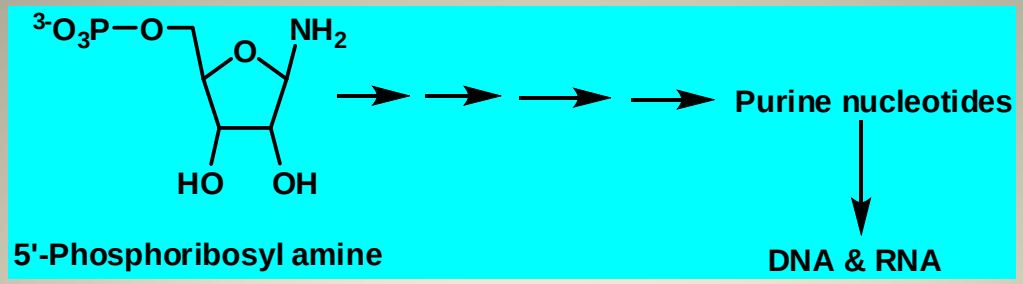
# A. Purine Antagonists

- **Those are group of compounds which are structurally related to the natural purine bases (hypoxanthine, adenine, xanthine and guanine) and compete with their cellular functions.**
- **They are proved to inhibit aminotransferase, adenylsuccinate synthase, adenylsuccinate lyase and inosine monophosphate dehydrogenase enzymatic systems leading to protein synthesis inhibition followed by cell death.**

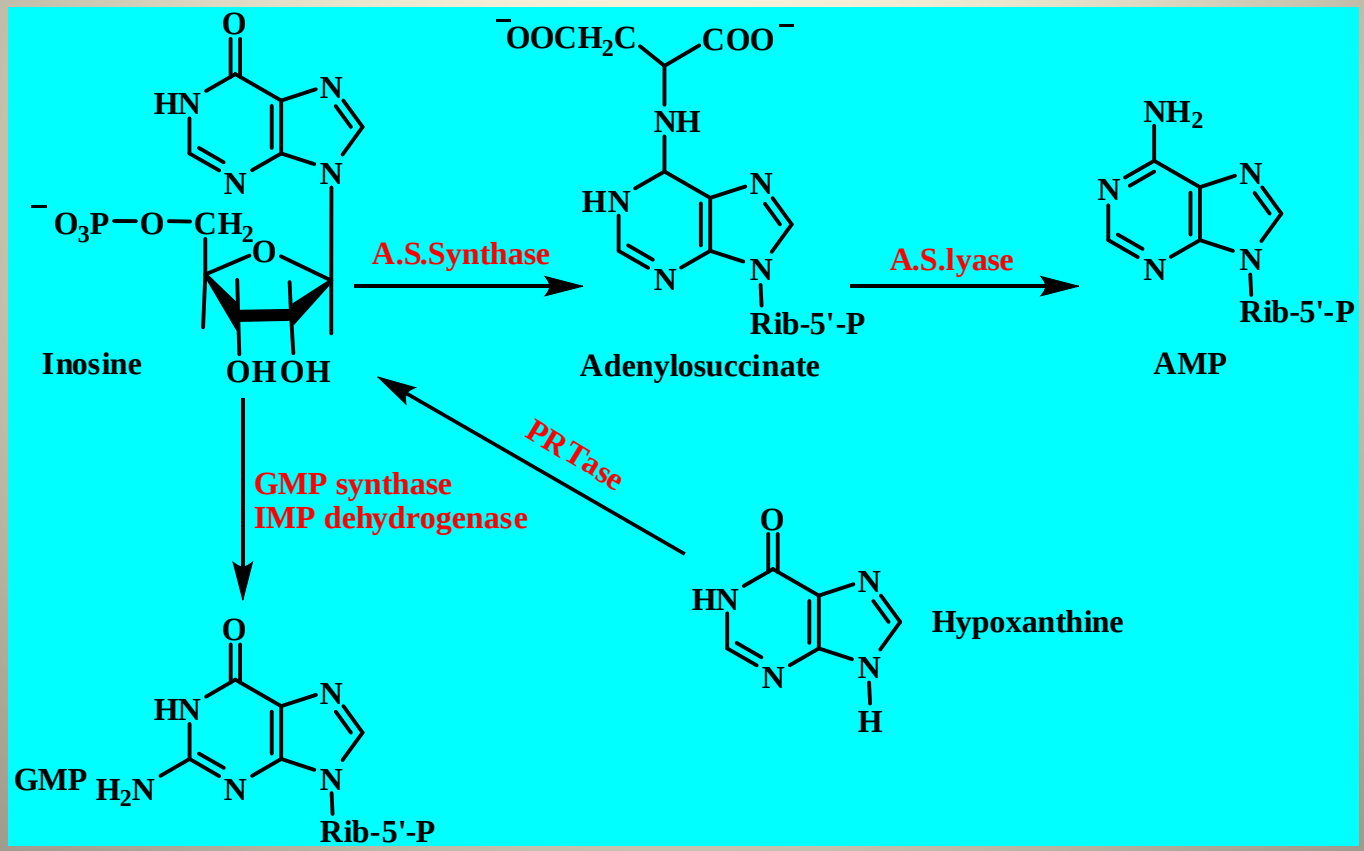



- **Normal cell can get its need from these bases through:**
  - **De Novo Purine Synthesis**
  - **Salvage Purine Synthesis**

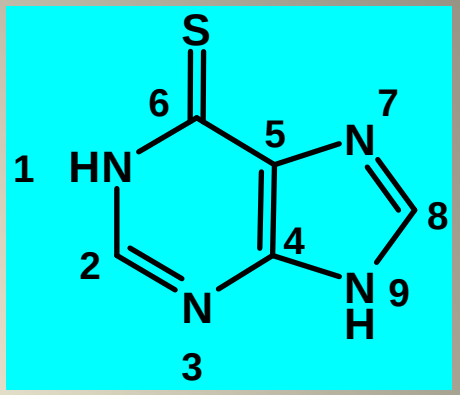
# De Novo Purine Synthesis




# Salvage Purine Synthesis

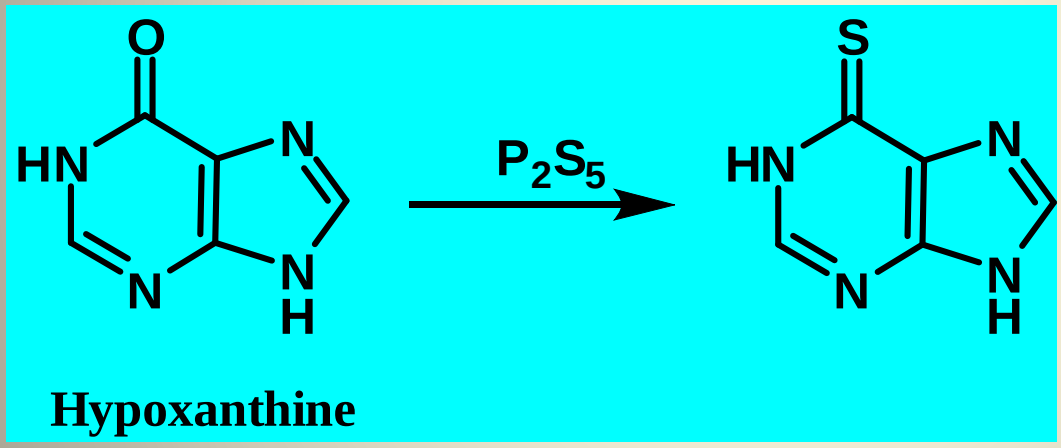


# 1. Mercaptopurine, Lukerine



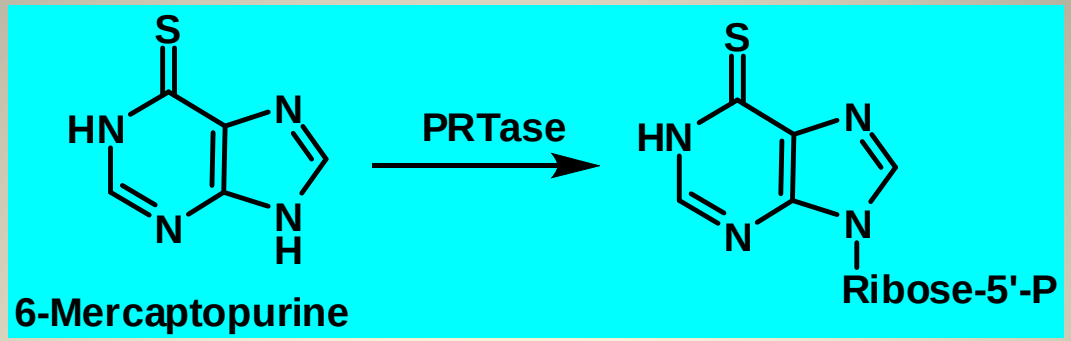

**6-Mercaptopurine or purine-6-thiol.**

**Synthesis**

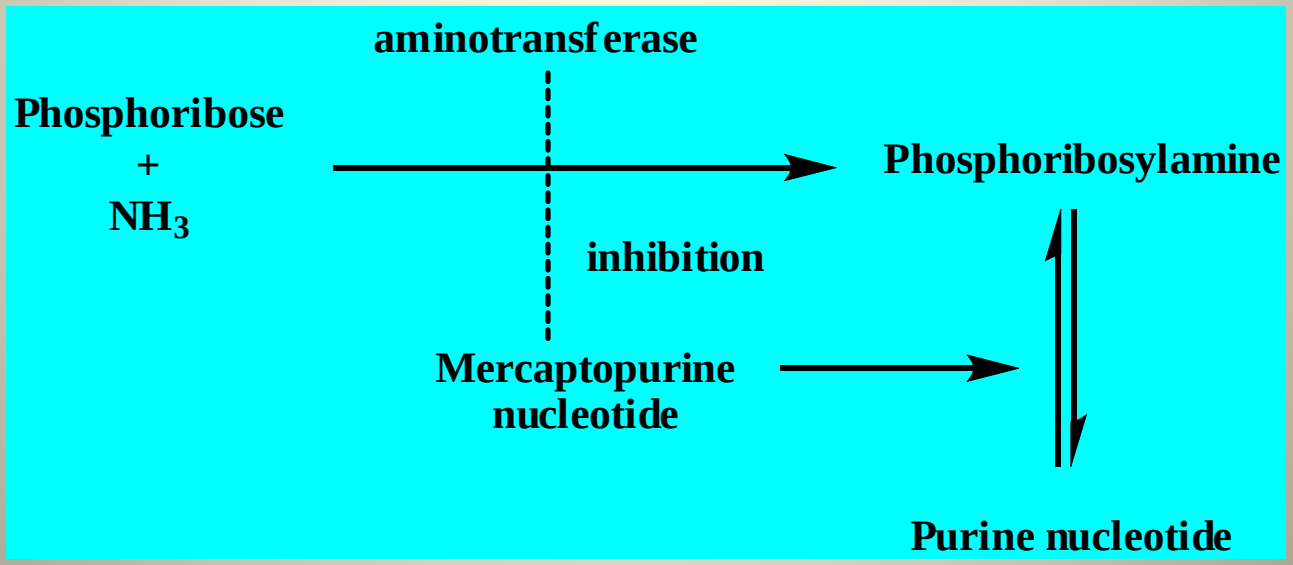



**Hypoxanthine**

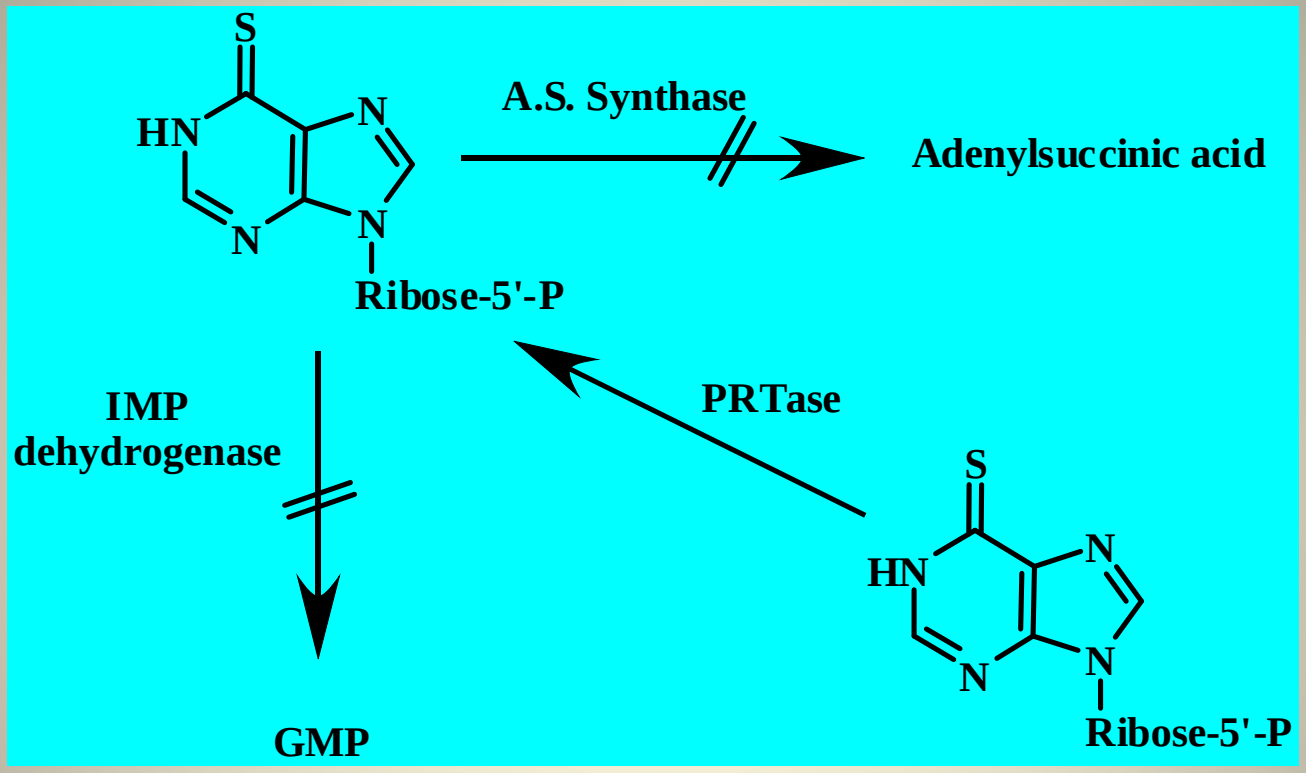
# Mechanism of Action



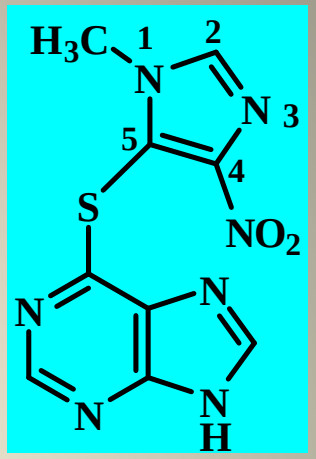

## 1. Inhibition of De Novo Synthesis



## 2. Inhibition of Salvage Purine Synthesis

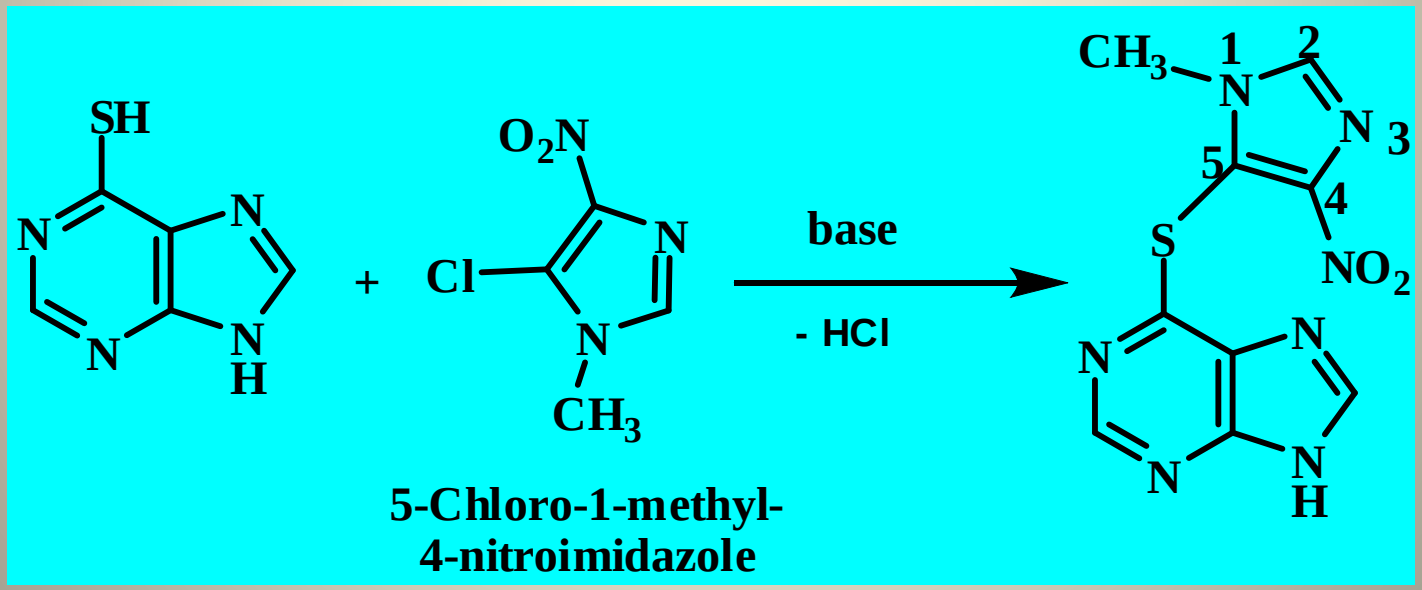


## 2. Azathioprine, Imuran




**6-[(1-Methyl-4-nitroimidazol-5-yl)thio]purine**

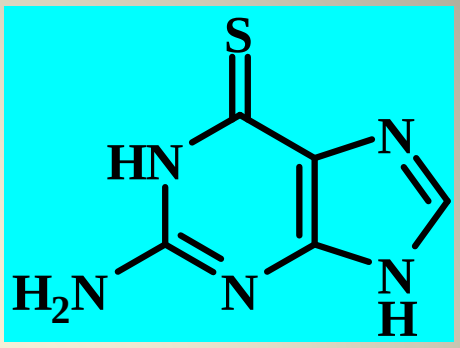
**Synthesis**




**5-Chloro-1-methyl-4-nitroimidazole**

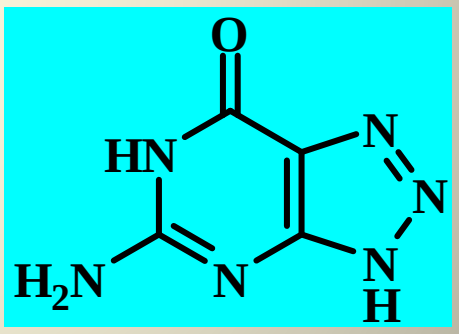
## 3. Thioguanine

**2-Amino-6-mercaptopurine**



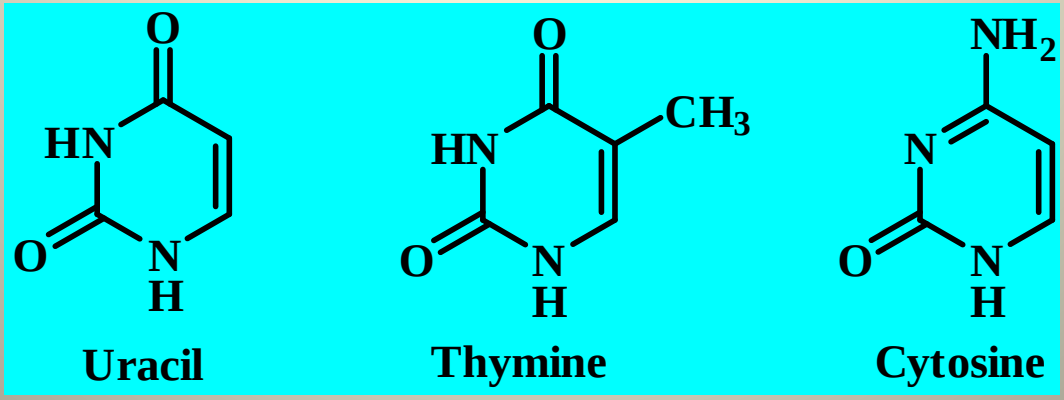

## 4. Azaguanine, Guanazole

**2-Amino-6-hydroxy-8-azapurine**

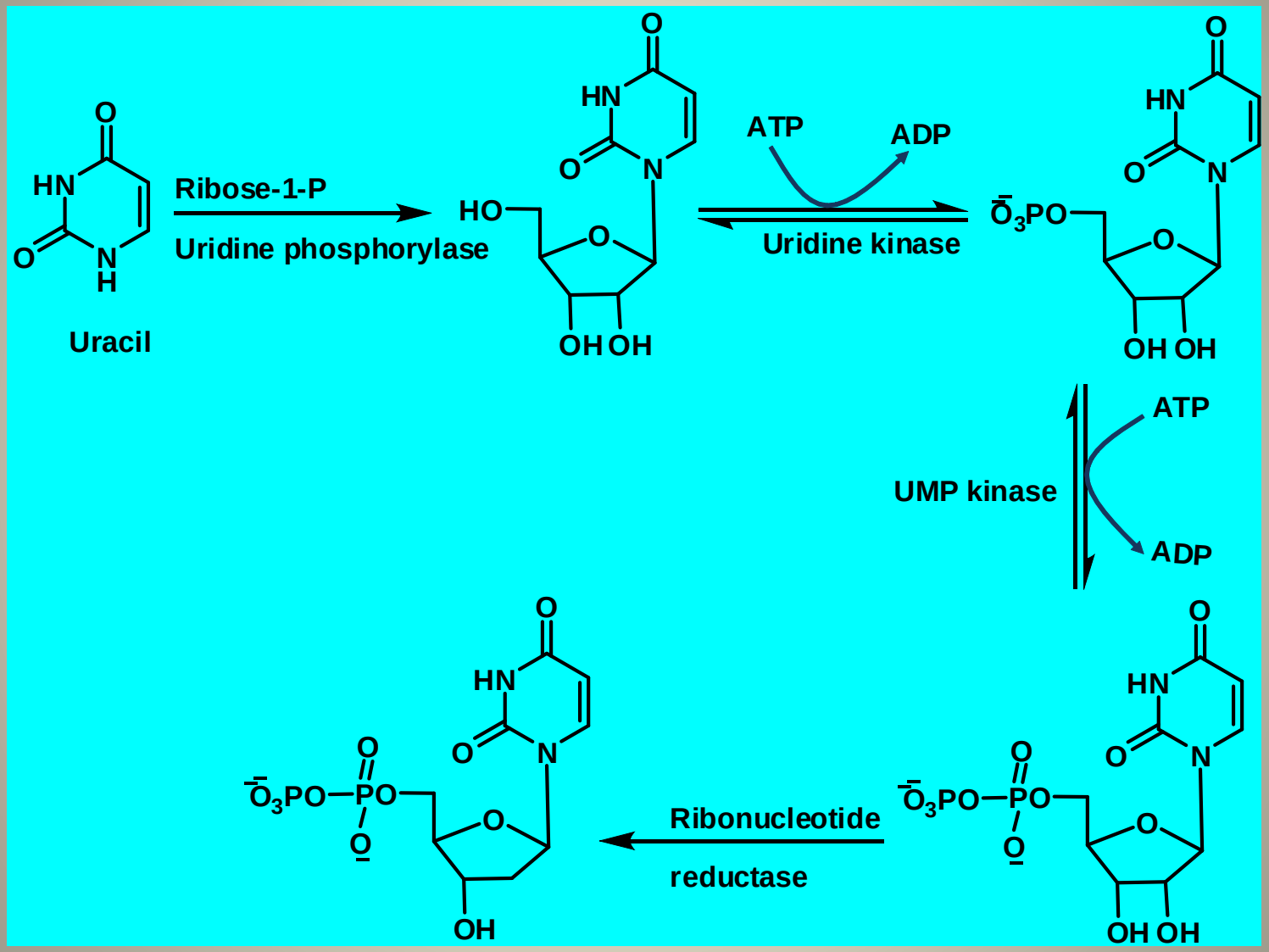


# B. Pyrimidine Antagonists

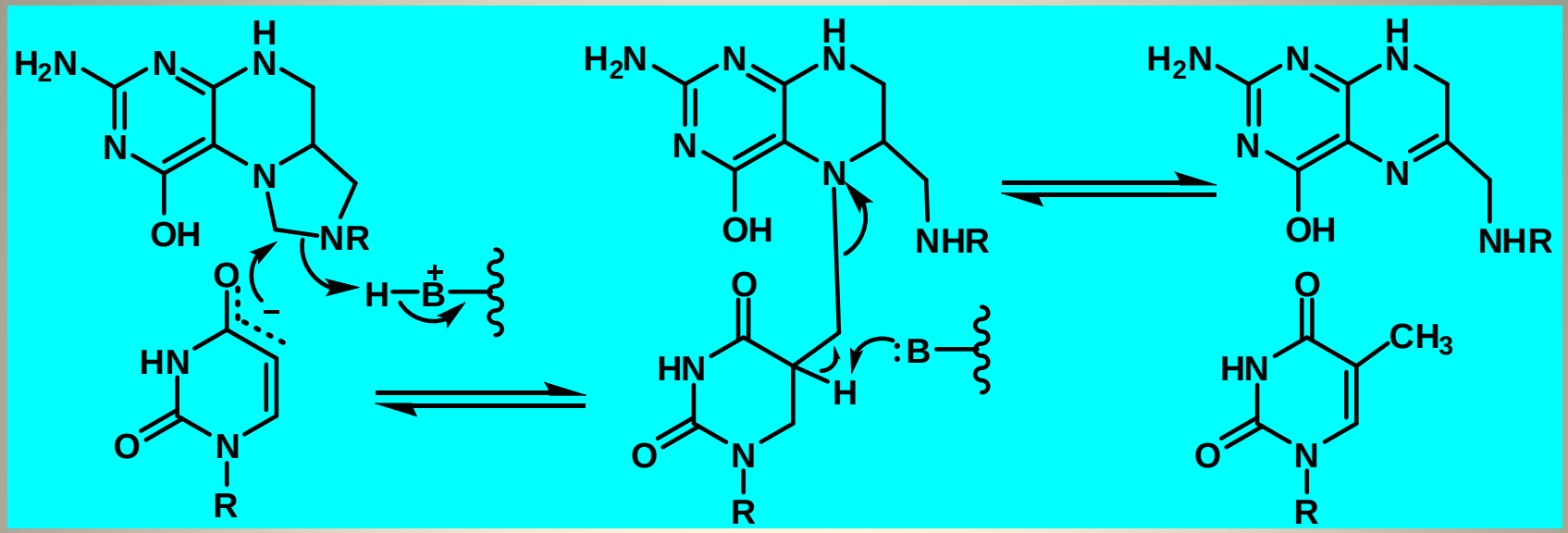
- **They resemble the natural pyrimidine (uracil, thymine and cytosine) in structures and compete with their cellular functions leading to the inhibition of two vital enzymatic systems responsible for the production of thymine from uracil.**
- **These two enzymes are Ribonucleotide Reductase and Thymidylate Synthase.**
  - **The metabolic role of ribonucleotide reductase in the production of deoxysugars.**
  - **The metabolic role of thymidylate synthase in the production of thymidine from uridine.**



# The metabolic role of Ribonucleotide Reductase enzyme

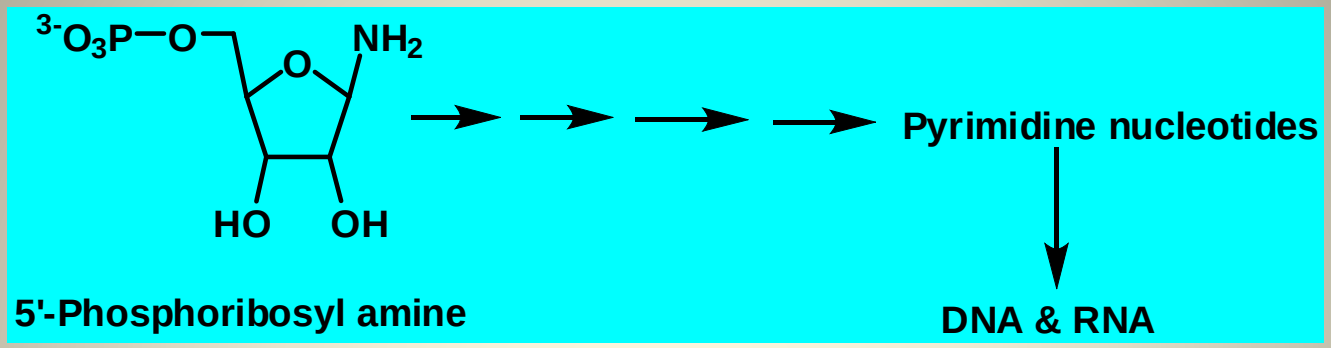


# The metabolic role of Thymidlate Synthase enzyme

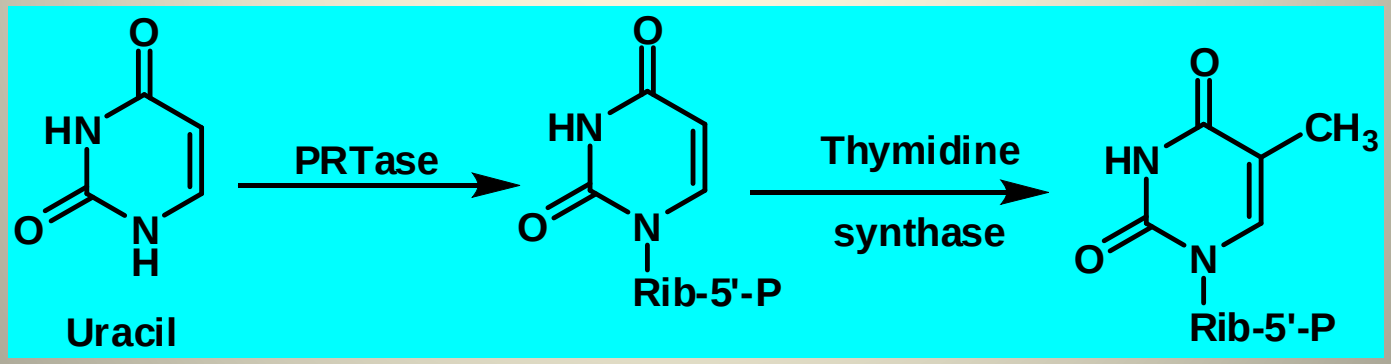


- **Normal cells can get its need from these bases through:**

## De Novo Pyrimidine Synthesis



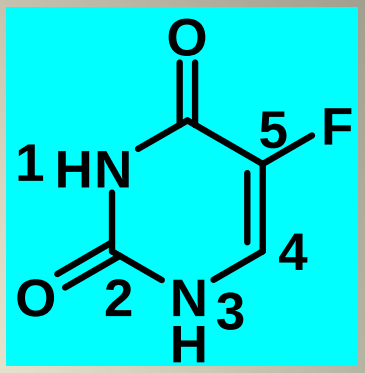

## Salvage Pyrimidine Synthesis



# 1. Fluorouracil, Fluoroplex

**5-Fluorouracil**

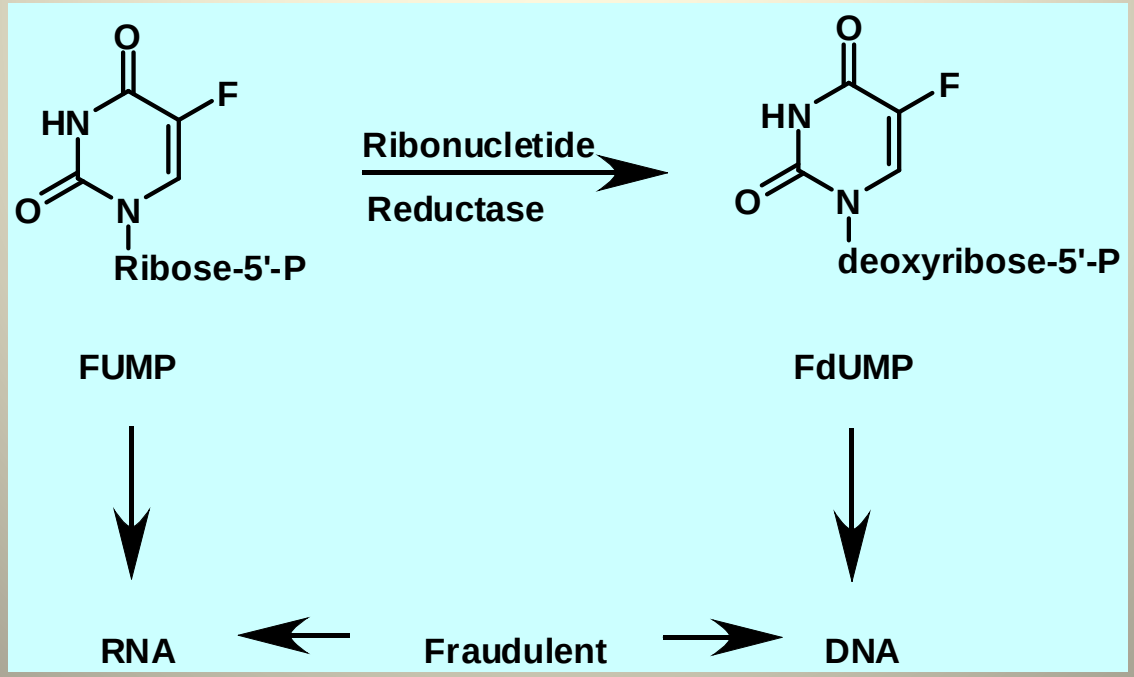
**5-Fluoro-2,4 (1*H*, 3*H*)-pyrimidindione.**

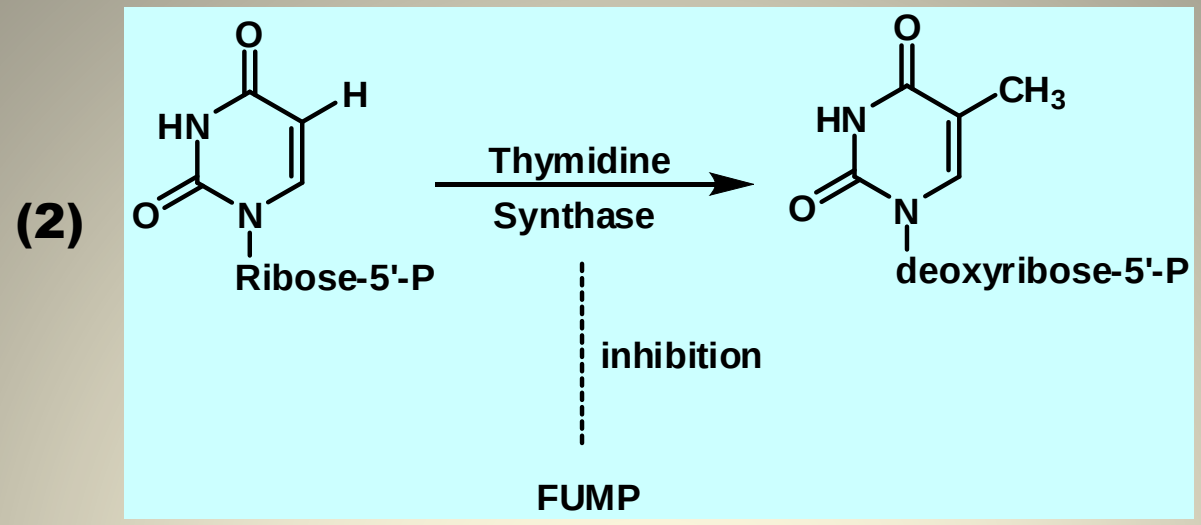


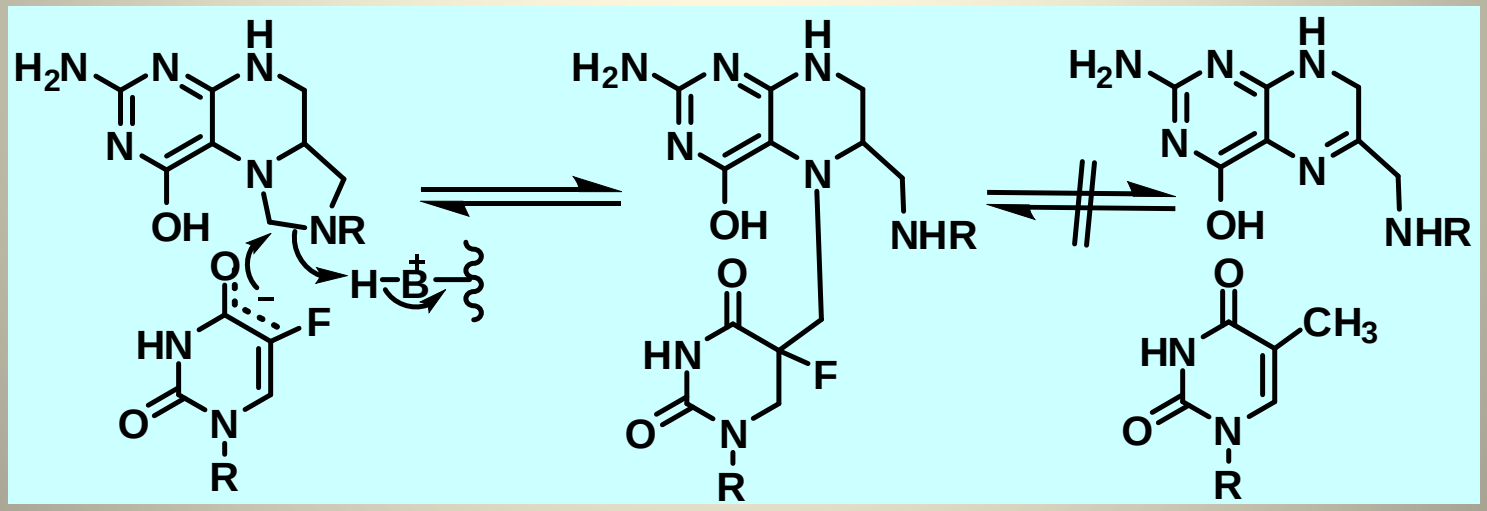

## Mode of action

**5-Fluorouracil is multimodal, exerting its effect by more than one mode**

**(1)**

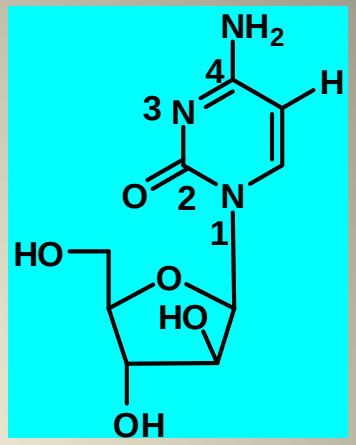




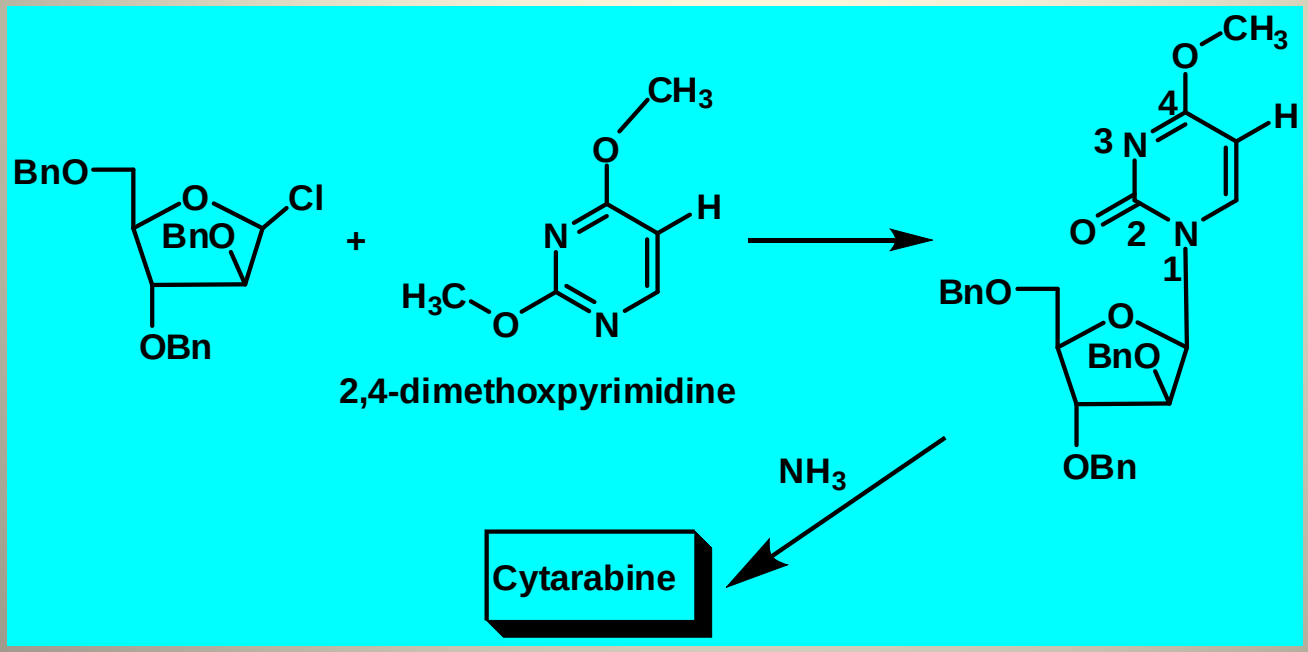
**Proposed mechanism for the inactivation of thymidylate synthase by 5-fluoro-2'-deoxyuridylate.**

# 2. Cytarabine, Cytosar

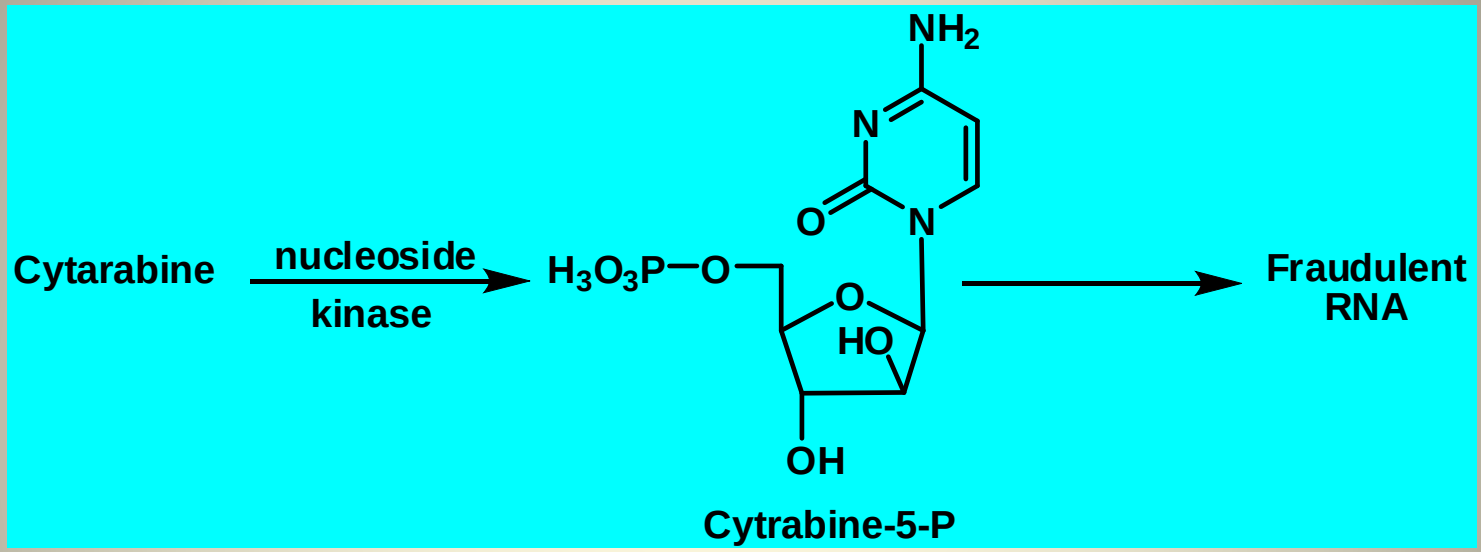



**4-Amino-1-*B*-D-arabinofuranosyl-2(1*H*)-pyrimidinone**

**Synthesis**



# Mode of Action



# C. Folic Acid Antagonists

- **Folic acid metabolism is an important source for one carbon moiety needed to convert uracil into thymine.**
- **Inhibition of folic acid metabolism, (inhibition of dihydrofolate reductase) deplete the biological systems from thymine –a pyrimidine base- very much needed for nucleic acid biosynthesis.**
- **Folic acid antagonists could be classified into:**

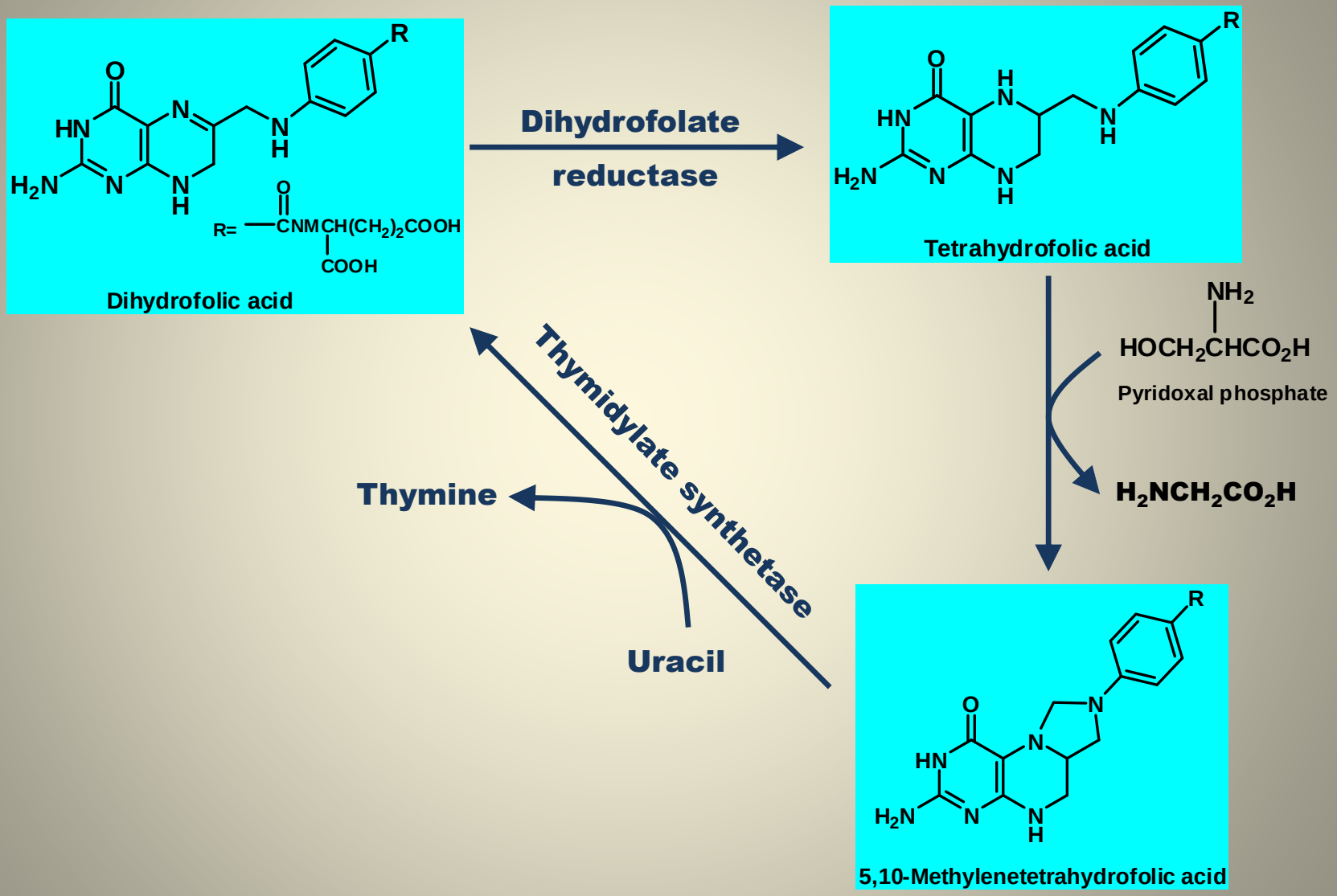
**A. Dihydrofolate reductase inhibitors**

**Methotrexate**

**B. Thymidylate synthetase inhibitors**

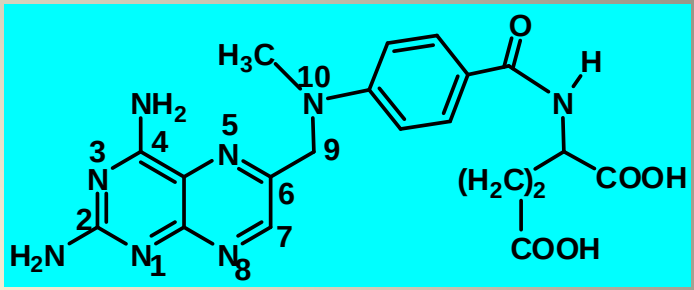
**5-Fluorouracil, Fluoroplex**

# The metabolic role of Dihydrofoalte Reductase enzyme

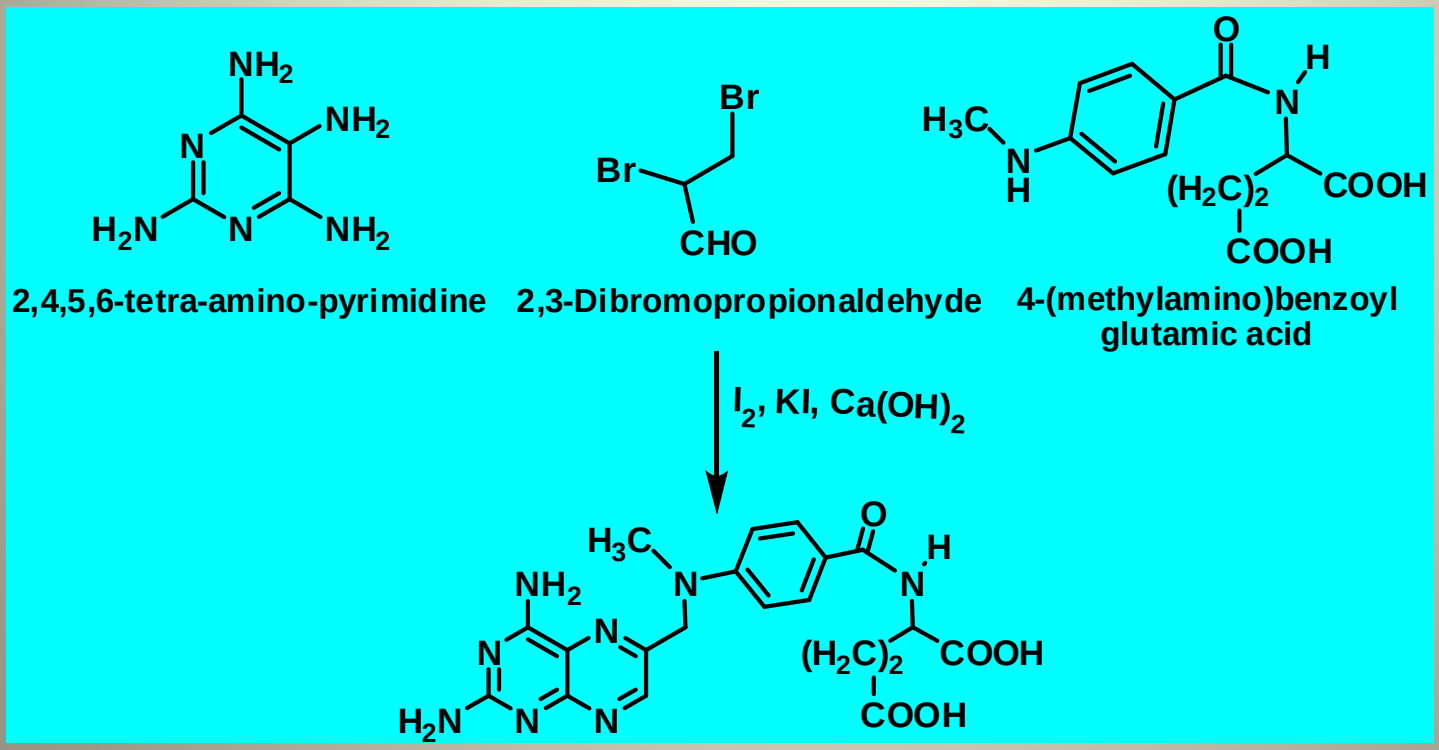


# 1. Methotrexate, Mexate, Amethopterin

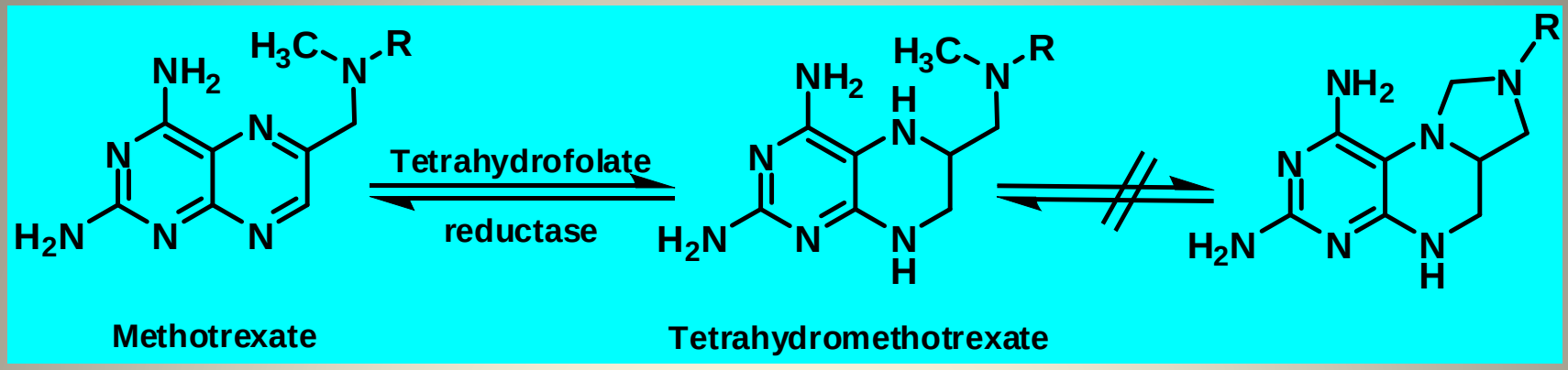
**4-Amino-10-methylpteroylglutamic acid**




## Synthesis



# Mode of Action




## Contraindications:

**Salicylates and sulfonamides increase methotrexate toxicity by:**

1. **Inhibiting its renal tubular secretion.**
2. **They displace methotrexate from plasma protein binding.**

## 2. Fluorouracil, Fluoroplex

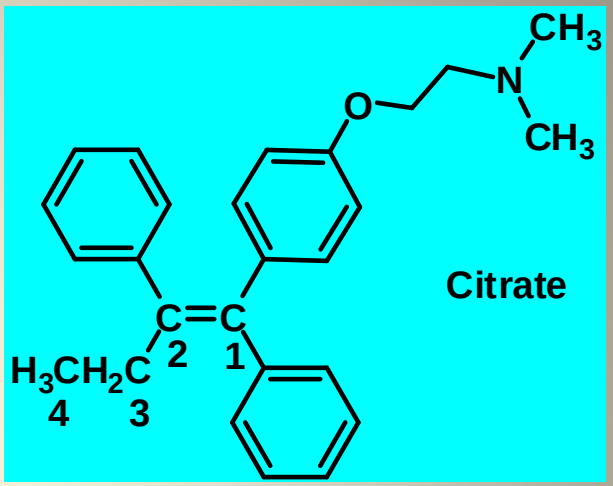
**As discussed before**

# III. Hormones

- **Some cancers are responsive to sex hormone treatment.**
- **Hormones control the dissemination of cancer but suffer from side effects as:**
    1. **Androgens → musculinizing effect**
    2. **Estrogens → feminizing effect**
    3. **Adrenocorticoids → salt and water retention**
- **Tamoxifen citrate is a nonsteroidal drug with anti-estrogenic effect used as anticancer**

# Tamoxifen citrate, Nolvadex

**2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine citrate.**




## Mode of Action

- **Tamoxifen is an estrogen receptor antagonist, blocks the growth promoting effects of estrogen on tumors.**
- **Uses: Advanced breast carcinoma.**

# Summary of Anticancer Drug Mechanisms and Sits